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CYTOLOGY OF OVARIAN TUMORS

ROBERT C. PAGE, M.D.
Fellow in Pathology, Mayo Foundation
AND
WILLIAM CARPENTER MacCARTY, M.D.*
ROCHESTER, MINN.

The malignant cell differs from the normal cell and from the reparative regenerative cell in several respects, two of the main points of difference being in the characteristics of the nucleus and nucleolus. In order to observe these structures with the least amount of distortion the tissue must not be dehydrated and embedded (MacCarty)[1]. Sections should be cut from fresh tissue or from formaldehyde-fixed tissue by the frozen section method of Wilson.[2]

The normal adult cell in most instances contains a relatively small nucleus with a very small or even invisible nucleolus. Notable exceptions are the cell of the ovum or that of nerve tissue, particularly the ganglion cell, each of which contains a large nucleus and one or more easily visible nucleoli. Normal cells, being differentiated, have a definite tissue polarity which makes up the normal architecture of the tissues and organs. Reparative regenerative cells, being partially differentiated, retain their anatomic position in the tissue. The component parts of these cells are more delicate than those of the malignant cells. The granules are smaller than those in malignant cells (MacCarty[3]), and the outlines are more delicate. The reparative regenerative as well as the malignant regenerative cell contains one or more nucleoli, and usually those of the malignant cell are much larger in proportion to the nucleus than are those of the reparative cell. All malignant cells arise from regenerative cells of normal tissue (MacCarty), and the pathologist must therefore be able to distinguish malignant cells even if these are few or if only a single malignant cell is present in tissue containing regenerative and normal cells if he is to diagnose cancer in its earliest form.

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*From the Division of Surgical Pathology, Mayo Clinic.

1. MacCarty, W. C.: J. Cancer Research **13**:167, 1929.
2. Wilson, L. B.: J. A. M. A. **45**:1737, 1905.
3. MacCarty, W. C.: Arch. Clin. Cancer Research **1**:3, 1925.

Many observations have been made on benign and malignant tissues concerning the relative sizes of nuclei and nucleoli since the original work was published (MacCarty [4]). The tissues studied have been breast, intestine and lymph nodes (MacCarty and Haumeder [5]); an adrenal tumor (Strohl [6]); stomach, breast, intestine, uterus and skin (Naidu [7]) and endometrium (McCormack [8]).

In this study an attempt was made to determine the relative nuclear and nucleolar areas and the nuclear-nucleolar ratios of ovarian tumors (cystadenoma, papillary cystadenoma and various malignant ovarian tumors).

METHOD OF STUDY

Representative blocks of tissue were taken from specimens of eighty-two ovarian tumors which had been removed by operation at the Mayo Clinic during the period 1933-1936 and fixed in solution of formaldehyde U. S. P. The tissues were cut by the frozen section method (Wilson) and stained with hematoxylin and eosin. Individual cells that were diagnostic for the particular type of tumor were studied. Twenty nuclei and their contained nucleoli in such cells from each section were studied under the oil immersion lens (Spencer objective, 1.8 mm.; numeric aperture, 1.25; tube length, 150 mm.; ocular, 10×). The shadows of the nuclei and nucleoli were projected through a constant distance onto a paper by means of a camera lucida and were then carefully traced. The nucleoli were again enlarged (Spencer objective, 48 mm.; numerical aperture, 0.08; tube length, 250 mm.; ocular, 1×), and the projected areas of the nuclei and nucleoli were measured with the planimeter.

These projected areas were then corrected to allow for microscopic and camera lucida magnification and also for the planimeter constant. The tracings of a stage micrometer of known measurement were projected, traced and measured, thus giving the microscopic and camera lucida magnification. The planimeter constant was obtained by measuring a square 2 by 2 cm., thus determining the actual area measured by a planimeter unit. To obtain the actual area of the nuclei and nucleoli, the planimeter reading in units of the enlarged tracing was multiplied by the planimeter constant, and the result was divided by the square of the magnification. This gave the area in square microns (figs. 1, 2, 3 and 4).

RESULTS

For cystadenoma the average area of a nucleus was 29.56 square microns, and for papillary cystadenoma it was 27 square microns; for the group of malignant tumors the average nuclear area was 44.6 square microns. This gave a nuclear ratio of malignant to nonmalignant tumor cells of 1.35:1 (table 1).

For cystadenoma the average area of the nucleoli was 0.63 square micron, while for the papillary cystadenoma it was 0.72 square micron.

4. MacCarty, W. C.: Surg., Gynec. & Obst. **41**:783, 1925. MacCarty.[3]
5. MacCarty, W. C., and Haumeder, Eva: Am. J. Cancer **20**:403, 1934.
6. Strohl, E. L.: Proc. Staff Meet., Mayo Clin. **10**:353, 1935.
7. Naidu, V. R.: Proc. Staff Meet., Mayo Clin. **10**:356, 1935.
8. McCormack, C. J.: Proc. Staff Meet., Mayo Clin. **10**:24, 1935.

The average nucleolar area of malignant tumor cells was 3.14 square microns. The ratio of the nucleolar area of the malignant to that of the nonmalignant cell was 3.9:1 (table 1).

The average nuclear-nucleolar ratio for cystadenoma was 46.9:1, whereas that for papillary cystadenoma was 37.5:1. The nuclear-

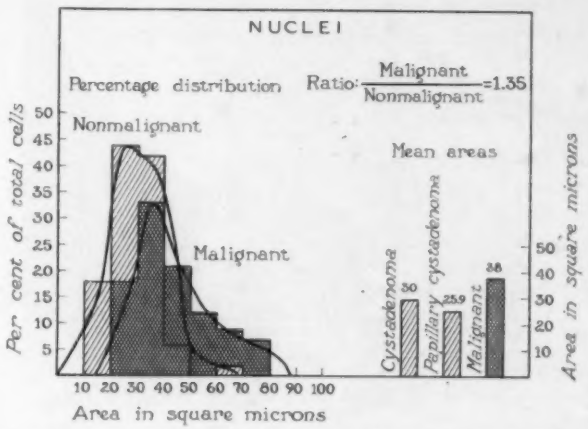

Fig. 1.—Comparison of the mean areas of the nuclei of malignant and nonmalignant cells in eighty-two ovarian tumors.

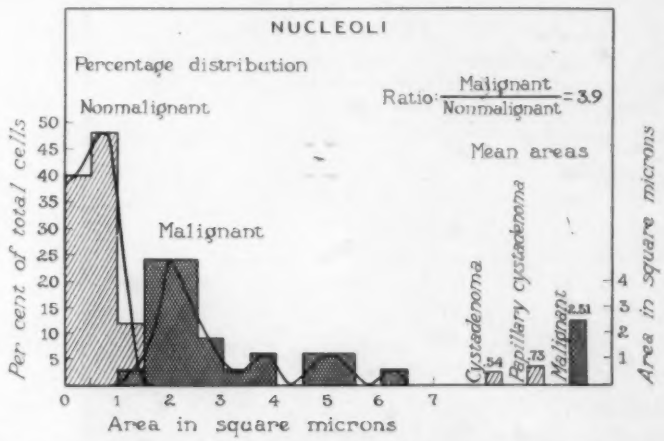

Fig. 2.—Comparison of the mean areas of the nucleoli of malignant and nonmalignant cells.

nucleolar ratios for the whole group of malignant tumors was 13.48:1 (table 1).

From a comparison of the grade of malignancy with the nuclear-nucleolar ratio (table 2) it was found that tumors of grade 1 (lowest

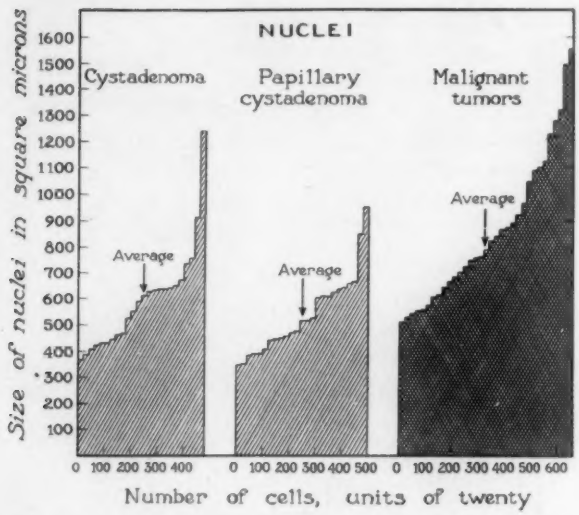

Fig. 3.—Comparison of the mean areas of the nuclei of malignant and non-malignant cells.

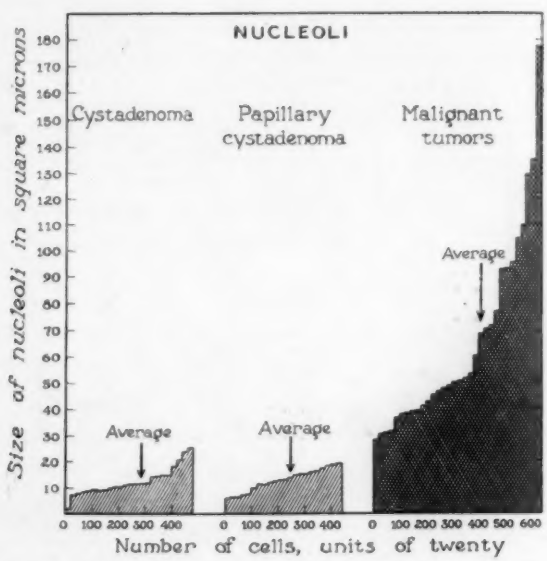

Fig. 4.—Comparison of the mean areas of the nucleoli of malignant and non-malignant cells.

grade of malignancy) had the highest ratio (16.19:1). Tumors of grade 4 (highest grade of malignancy), on the other hand, had the lowest nuclear-nucleolar ratio (10.14:1). Tumors of grades 2 and 3 showed ratios of 12.13:1 and 14:1, respectively.

In the malignant group, the average nuclear-nucleolar ratio for each type of tumor was determined (table 3). The lowest ratio, 12:1, was for sarcoma, while the highest, 18:1, was for solid tumors. The other malignant tumors were between these extremes. The extremes

TABLE 1.—*Comparison of Malignant and Nonmalignant Tumors of the Ovary*

Tumor	Cases	Nuclear-Nucleolar Ratio	Average Size, Square Microns	
			Nucleus	Nucleolus
Cystadenoma	24	46.9 : 1	29.56	0.63
Papillary cystadenoma	25	37.5 : 1	27	0.72
Malignant ovarian tumor	33	13.48: 1	44.6	3.14

TABLE 2.—*Comparison of Grade of Tumor with Nuclear-Nucleolar Ratio*

Grade	Cases	Nuclear-Nucleolar Ratio
1	10	16.19 : 1
2	16	12.13 : 1
3	5	14 : 1
4	2	10.14 : 1

TABLE 3.—*Comparison of Malignant Tumors of the Ovary*

Type of Tumor	Cases	Nuclear-Nucleolar Ratio	Average Size, Square Microns	
			Nucleus	Nucleolus
Papillary cystadenocarcinoma	17	13.7 : 1	46.81	3.4
Solid tumor	7	18.1 : 1	42.42	2.34
Sarcoma	1	12.0 : 1	42.3	3.5
Adenocarcinoma	6	12.5 : 1	43.2	3.44
Folliculoma	2	12.4 : 1	35	2.82

of the ratio for cystadenoma were found to be 82.9:1 and 24.2:1. The extremes for papillary cystadenoma were 87.2:1 and 23.7:1. The extremes for the malignant group were 23:1 and 8.39:1. The largest ratio for the malignant tumors was 23:1, in a papillary cystadenocarcinoma, whereas the smallest ratio for the nonmalignant group was 23.7:1, in a papillary cystadenoma. In this group of ovarian tumors not a single case of overlapping of ratios in the malignant and nonmalignant groups was found (figs. 5 and 6).

These observations show that the nuclear-nucleolar ratio is much smaller in malignant than in nonmalignant tumors. The value of the size of the nucleus and of the nucleolus as a diagnostic aid in the early

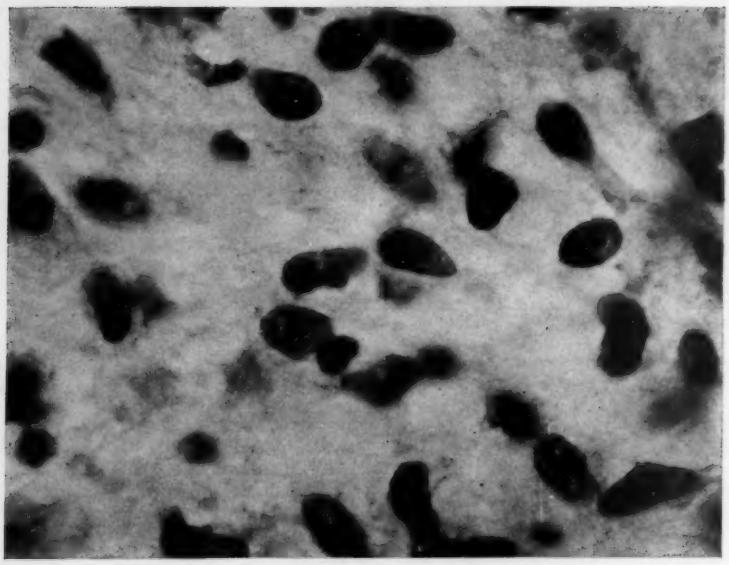

Fig. 5.—Sarcoma of the ovary, showing single and multiple nucleoli in nuclei (hematoxylin and eosin; × 800).

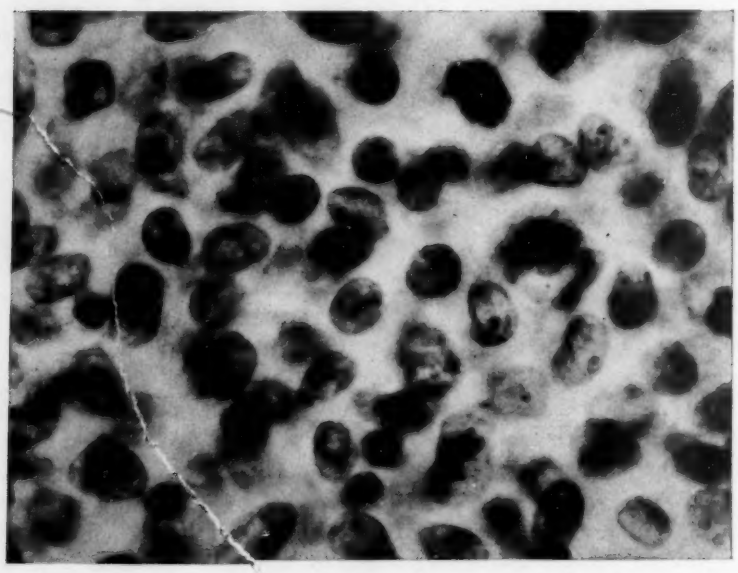

Fig. 6.—Folliculoma of the ovary showing large nucleoli in the nuclei (hematoxylin and eosin; × 950).

detection of cancer has been proved. The pathologist must, however, know the relative sizes of these structures in normal tissue and in benign tumors before he can use them as diagnostic criteria in the detection of early malignancy. Each individual tissue and tumor has its own particular nuclear-nucleolar ratio, which must be known.

In ovarian tumors the size of the nucleolus was found to be more diagnostic of malignancy than the size of the nucleus. In malignant tumors the average nucleolus was found to be four times the size of the nonmalignant nucleolus; the average nuclear area of the malignant cell was slightly less than one and a half times that of the nonmalignant cell.

SUMMARY

Studies of nuclei and nucleoli were made on typical cells of a group of thirty-three malignant and forty-nine nonmalignant tumors of the ovary. By determining the actual areas of the nuclei and nucleoli, it was found that the ratio of the area of the nucleus of the malignant cell to that of the nonmalignant cell was 1.35:1. The ratio of the area of the nucleolus of the malignant cell to that of the nonmalignant cell was 3.9:1.

The nuclear-nucleolar ratio of the malignant cell was found to correspond to the grade of malignancy in that as the grade of malignancy increases, the nuclear-nucleolar ratio becomes smaller. The nuclear-nucleolar ratio of malignant tumors of the ovary is less than a third that of nonmalignant tumors.

This study again emphasizes the value of a knowledge of the cytology of malignant and nonmalignant tissues, which enables one to make a diagnosis in the early stages of cancer.

INFLUENCE OF DUSTS ON TUBERCULOUS INFECTION

SUSCEPTIBILITY OF SUBCUTANEOUS LESIONS PRODUCED BY DUSTS TO INFECTION BY TUBERCLE BACILLI INJECTED INTRAVENOUSLY

ARTHUR J. VORWALD, PH.D., M.D.
SARANAC LAKE, N. Y.
AND
ARTHUR LANDAU, M.D.*
CAPETOWN, UNION OF SOUTH AFRICA

The influence of dust on the susceptibility of tissues to infection by the tubercle bacillus is a problem of paramount importance in pneumonoconiosis. It has been shown clinically and pathologically [1] that prolonged inhalation of silicious dust in high concentrations is attended by a marked increase in the morbidity and mortality from pulmonary tuberculosis. Gardner [2] has repeatedly demonstrated that when animals exposed to silica dust are made to inhale an attenuated strain of tubercle bacilli of the human type, R_1, progressive pulmonary disease develops in them. This susceptibility attends the inhalation of dusts high in silica, such as quartz,[3] chalcedony [4] and granite.[5] Dusts low in silica,

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* Dorothy Temple Cross Research Fellow in Tuberculosis, England.

From the Saranac Laboratory for the Study of Tuberculosis of the Edward L. Trudeau Foundation.

1. Collis, E. L.: Pub. Health **28**:252, 1914-1915; **29**:11, 1915. General Report of the Miners' Phthisis Prevention Committee, Johannesburg, March 15, 1916, Pretoria, South African Government Printing & Stationery Office, 1916. Irvine, L. G.; Simson, F. W., and Strachan, A. S.: The Clinical Pathology of Silicosis, in Silicosis: Records of the International Conference held at Johannesburg, International Labour Office Studies and Reports, Series F (Industrial Hygiene) no. 13, Boston, World Peace Foundation, 1930, p. 269. Gardner, L. U.: Am. Rev. Tuberc. **29**:1, 1934. Lanza, A. J., and Vane, R. J.: ibid. **29**:8, 1934. Riddell, A. R.: ibid. **29**:36, 1934. Sayers, R. R.; Meriwether, F. V.; Lanza, A. J., and Adams, W. W.; Silicosis and Tuberculosis Among Miners of the Tri-State District of Oklahoma, Kansas and Missouri, Technical Paper 545, United States Department of Commerce, Bureau of Mines, 1928, p. 1; Technical Paper 552, 1933, p. 1.

2. Gardner, L. U.: Am. Rev. Tuberc. **25**:8, 1932. Cummings, D. E.: ibid. **26**:4, 1932.

3. Gardner, L. U.: Am. Rev. Tuberc. **20**:833, 1929.

4. Unpublished data of the Saranac Laboratory.

5. Gardner, L. U.: Am. Rev. Tuberc. **4**:734, 1920; footnote 3.

such as hematite [6] and crude fluorspar,[7] and nonsilicious dusts, such as marble,[8] coal [9] and gypsum,[10] have no such effect. Silica is therefore apparently specific in predisposing pulmonary tissue to infection by the tubercle bacillus.

As yet there is no recognized explanation for this activity. It has been attributed to the fact that silica induces fibrosis, the fibrous tissue being considered more susceptible than normal tissue to infection by the tubercle bacillus. Others [11] maintain that the fibrosis causes mechanical obstruction to the lymphatics, thus retarding elimination of bacilli and predisposing the lung to tuberculosis. Many observers are of the opinion, however, that fibrosis is of little significance and that the most important determining factor is the chemical character of the dust. Dusts high in free silica are considered active in that of themselves or by interaction with the tissue they afford a more favorable medium for increased growth of the tubercle bacilli. It has been shown by Price [12] and confirmed in this laboratory that when silica is added to the artificial culture medium growth of the organisms is stimulated. Kettle [13] demonstrated that subcutaneous lesions due to the presence of silica are favorable foci for the localization and proliferation of intravenously injected bacilli. Such proliferation did not occur in lesions produced by nonsilicious dusts or by other irritating agents, such as turpentine and calcium chloride. This technic was advocated by Kettle as a method for testing the capacity of a dust to modify an infection.

In the experiments under discussion the technic employed by Kettle has been used to test the action of a considerable number of industrial dusts for the purpose of determining their influence on tuberculous infection. It was also hoped that the series might demonstrate whether silica must exist in a free state to exert its specific stimulating effect and whether the presence of contaminating nonsilicious materials modifies its action.

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6. Gardner, L. U.: Pathology of Silicosis, in Kuechle, B. E.: Second Symposium on Silicosis, Wausau, Wis., Employers Mutual Liability Insurance Co., 1935.

7. Unpublished data of the Saranac Laboratory.

8. Gardner, L. U.: Am. Rev. Tuberc. **25**: 577, 1932.

9. Gardner, L. U.; Cummings, D. E., and Dowd, G. R.: J. Indust. Hyg. & Toxicol. **25**:6, 1933.

10. Gardner, L. U.: Internat. Clin. **2**:16, 1935.

11. Cummins, S. L.: Am. Rev. Tuberc. **29**:17, 1934.

12. Price, R. M.: Canad. J. Research **7**:617, 1932.

13. Kettle, E. H.: Brit. J. Exper. Path. **5**:158, 1924; J. Path. & Bact. **35**: 395, 1932.

METHODS

The dusts that were tested comprised free silica, both pure and mixed with other substances, various silicates and a few nonsilicious minerals. A list of the dusts used follows:

1. Quartz—a free crystalline silica

2. Crystabolite—a conversion form of normal quartz produced by heating to high temperatures

3. Tridymite—a conversion form of normal quartz produced by heating to high temperatures

4. Vitreous silica—a conversion form of normal quartz produced by heating to high temperatures

5. Silica 20 A°—a synthetic preparation of vitreous silica, composed of particles the maximum diameter of which is 20 angstrom units

6. Chalcedony—a cryptocrystalline form of silica, in which minute crystals of quartz are cemented together in a matrix of amorphous silica

7. Opal—a natural free silica, not crystalline but amorphous

8. Diatomaceous earth (diatomite)—an amorphous silica deposited as a silicious skeleton in diatomes

9. Granite—a natural mixture containing about one-third quartz and two-thirds feldspar and mica

10. Chert, ferruginous—a natural mixture of equal parts of iron oxide and cryptocrystalline silica in the form of chalcedony

11. Fluorspar, crude—calcium fluoride containing calcite and about 10 per cent quartz

12. Hematite—iron oxide containing 6 per cent free silica in the form of crystalline (quartz) and cryptocrystalline varieties

13. Feldspar (soda microcline)—an anhydrous silicate of potassium, sodium and aluminum

14. Synthetic zeolite (analcite)—a hydrated silicate of sodium and aluminum

15. Garnet—an anhydrous silicate of iron, aluminum and magnesium

16. Glauconite—a hydrous silicate of potassium, iron, aluminum and magnesium in the serpentine-talc division

17. Sericites O, T and C—sericites from three different sources. They are varieties of muscovite mica and are hydrous silicates of potassium and aluminum

18. Talc—a hydrous silicate of magnesium

19. Sillimanite—an anhydrous silicate of aluminum, belonging to the topaz group

20. Fluorspar, acid—a pure calcium fluoride

21. Aluminum oxide—a commercial product known as aloxite

22. Carborundum—a synthetic silicon carbide (sic)

The dust particles were ground to uniform size and varied from 1 to 3 microns in diameter. Five milligrams of each dust suspended in 0.25 cc. of physiologic solution of sodium chloride was injected subcutaneously into the abdominal wall, in seventy white mice. Well spaced injections, usually four in number, of one or more of the dusts to be tested, were made into each animal, including a control

injection of quartz. In this way it was always possible to compare the lesions produced by different dusts with each other and with a lesion produced by quartz in the same animal.

Tubercle bacilli, human strain H_{37}, were injected intravenously [14] in one group three days, in a second group seven days and in a third group fourteen days, after the subcutaneous injection of the dust. The doses used were 2.5 and 5 mg. of dust, each suspended in 0.25 cc. of sterile salt solution. The dosage and the interval of time elapsing between the injection of the dust and that of the bacilli were varied to determine the optimal conditions for bacterial proliferation.

The mice were put to death at intervals of from three to sixty-three days after infection. The subcutaneous lesions were excised from the abdominal wall, fixed in Zenker solution [15] containing acetic acid and embedded in paraffin. Sections were treated as a routine by the Ziehl-Neelsen method (Hopkin's modification) for the demonstration of tubercle bacilli. Sections of a lung, the liver and the spleen in each animal were also prepared to determine the extent of visceral disease.

EXPERIMENTAL OBSERVATIONS

On subcutaneous injection, the dust particles spread throughout the bleb formed by the injected fluid. This was best observed with heavily pigmented dusts, such as carborundum, hematite, garnet and chert. After twenty-four hours the bleb had disappeared, and the dusts were well localized in small subcutaneous foci. At this time there were no macroscopic differences in the character of the reactions. At a later period, usually after two weeks, the lesions produced by free silica were raised and slightly firmer than those caused by other dusts injected into the same animal.

Intravenous injection of tubercle bacilli produced no alteration in the gross appearance of the dust lesions; at least there was no consistent change indicative of bacillary localization. An occasional focus showed superficial ulceration, but this could not be attributed wholly to infection, for it also occurred in nontuberculous animals. It was interpreted as a result of extension of the reaction to the dust into the epidermis.

At autopsy, dissection demonstrated that the dust particles were usually confined to small nodular foci in the subcutaneous tissue. The details of the reaction to an individual dust are not pertinent to this paper. In general, each of the irritants produced an immediate exudation of lymphocytes, large mononuclear cells and few polymorphonuclear leukocytes. Later, however, the reactions to the dusts evolved as of two distinct types. All forms of free silica produced lesions characterized by necrosis and fibrosis. Each of these lesions exhibited a central

14. Intravenous injection is facilitated by keeping the mouse in a hot box at approximately 60 C. for from five to ten minutes. After such treatment the veins of the tail are engorged with blood and can be easily entered with a small gage needle.

15. The formula is: potassium bichromate, 2.5 Gm.; mercury bichloride, 5 Gm.; distilled water, 100 cc., and glacial acetic acid, 5 cc.

necrotic matrix with diffusely scattered dust particles and cells in various stages of degeneration, delimited by a wall of inflammatory cells and fibrous tissue. Mononuclear cells filled with dust and polymorphonuclear leukocytes were scattered throughout the wall and often grouped in small secondary nodules in the surrounding tissue. The late reactions to other dusts were represented in loosely packed mononuclear cells so filled with particles that their structure was often completely obliterated. Necrosis was not a conspicuous feature. In many instances a focus of dust was demarcated by a thick peripheral zone of inflammatory cells without evident fibrosis.

The dose of bacilli injected had little effect on the detection of organisms in the area of reaction to a particular irritant. The age of the lesion caused by a dust was likewise apparently of no significance. The duration of the infection, however, seemed to be of some importance, for organisms were not found in the lesions of mice killed within one week after the injection of the bacilli. In a necrotic focus, acid-fast bacilli were most often found in the peripheral portion of the dead tissue. In a lesion without necrosis, the organisms were intracellular but not localized in any particular portion. The number of bacilli varied considerably in different parts of the same dust focus and in different foci in the same animal. In general, bacilli were more numerous and often occurred as clumps in lesions produced by various forms of pure silica and by the natural mixture, granite. In the reactions to the silicates and nonsilicious minerals, the bacilli were usually scattered and in most cases difficult to find. Even these differences were not invariable. For example, the only zeolite focus positive for organisms contained more bacilli than the quartz control area in the same animal. This was also true in one of the crude fluorspar and one of the acid fluorspar foci.

The results are summarized in tables 1, 2 and 3. Table 1 shows the various dusts that were used, the silica content of each and its form, also the presence or absence of necrosis in the lesions and the percentage of dust foci positive for tubercle bacilli. The presence of bacilli in any one of the four or more dust foci in the subcutaneous tissue of an animal was considered sufficient proof of a satisfactory intravenous inoculation. If by accident the infection had been subcutaneous, visceral tuberculosis would have developed just as readily, but it seems unlikely that organisms would be carried to the subcutaneous dust foci so remote from the site of inoculation. In twelve animals there was no evidence of tuberculosis. Nine of these died within the first week after infection. In the remaining three, put to death at twenty-one, twenty-one and thirty-nine days, respectively, after infection, intravenous inoculation was apparently not accomplished. In eight other animals all the dust foci were negative for bacilli, although

visceral disease was present. The lesions in these animals have not been included in the tables.

Table 2 compares the effects of all forms of free silica, of mixtures of free silica and other forms, of silicates and of nonsilicious

TABLE 1.—*Comparison of Various Forms of Minerals Used*

Mineral	Percentage of Total Silica	Percentage of Free Silica	Mineral Form	Total Number of Lesions	Lesions with Necrosis	Lesions Positive for Bacilli	Percentage of Lesions Positive
Free Silica—Group 1							
Quartz	100	100	Crystalline	50	50	49	98
Crystabolite	100	100	Crystalline	6	6	3	50
Tridymite	100	100	Crystalline	5	5	3	60
Vitreous silica	100	100	Crystalline	6	2	6	100
Silica 20 A°	100	100	Crystalline	4	4	3	75
Chalcedony	100	100	Cryptocrystalline	7	3	4	56
Opal	90	90	Amorphous	10	10	5	50
Diatomaceous earth	90	90	Amorphous	7	6	1	14
Free Silica Mixed with Other Minerals—Group 2							
Granite	71	30	Crystalline	3	3	3	100
Chert	50	50	Cryptocrystalline	7	4	0	0
Fluorspar, crude	11	10	Crystalline	10	4	6	60
Hematite	6	5	Crystalline	6	0	0	0
Silicates—Group 3							
Feldspar	65	0	Crystalline	5	4	3	60
Synthetic zeolite	57	0	Crystalline	5	3	1	20
Garnet	53	0	Crystalline	6	4	0	0
Glauconite	49	0	Crystalline	5	1	0	0
Sericite O	45	0	Crystalline	2	2	1	50
Sericite T	45	0	Crystalline	2	2	1	50
Sericite C	45	0	Crystalline	2	1	1	50
Talc	43	0	Crystalline	3	2	1	33
Sillimanite	37	0	Crystalline	3	1	1	33
Nonsilicious Minerals—Group 4							
Fluorspar, acid	0	0	Crystalline	16	4	10	62
Aluminum oxide	0	0	Crystalline	4	0	2	50
Carborundum	0	0	Crystalline	5	0	0	0

TABLE 2.—*Comparison of Various Groups of Minerals Used*

Mineral	Total Number of Lesions	Percentage with Necrosis	Percentage Positive for Bacilli
Free silica group	95	90	77
Free crystalline	78	89	87
Free amorphous	17	94	35
Mixed group	26	42	34
Silicate group	33	60	27
Nonsilicious group	25	16	48

minerals. It emphasizes the high incidence of positive findings with free silica. If all forms of free silica are included, 88 per cent of the lesions were positive. If the forms of free silica are separated, as shown in the table, into crystalline and amorphous varieties, 87 per cent of the lesions with the former, and 35 per cent of those with the latter, were positive. Possibly the number of lesions with the latter was too small to permit statistical evaluation. In the case of the

mixed dusts the figures are unquestionably misleading, for they include granite foci, which were 100 per cent positive, as well as chert and hematite lesions, which were 100 per cent negative. The balance is made up of observations on crude fluorspar.

Table 3 records the estimated number of acid-fast tubercle bacilli observed in each focus of each dust. Because of the great number of organisms found in many of the lesions it was impossible to make an actual count. The estimated number was recorded as: scarce, 1; few, 2; numerous, 2, and very numerous, 4. It is to be noted that in all but one instance, mouse 6, the quartz focus was the positive one.

The number of observations on each mineral or even on each group of minerals, with the possible exception of the free silica group, is not sufficiently large to be statistically significant. A greater number of tests, to compensate for technical obstacles, are required.

In spite of these difficulties, the percentages of lesions positive for tubercle bacilli with the different types of minerals (tables 1 and 2) and the relative numbers of bacilli observed in these lesions (table 3) indicate a definite trend toward bacterial localization and proliferation in lesions produced by free silica either in pure form or when contaminated by other materials. The iron-containing minerals that have been tested constitute a notable exception, which is being investigated at the present time.

The various forms of crystalline-free silica did not seem to be equally potent as regards incidence of lesions positive for bacilli, and the numbers of bacilli in different foci of the same mineral varied considerably. There seems to be no particular reason why this should be so. All the forms produce necrosis followed by fibrosis. The cryptocrystalline-free silica, chalcedony, when present in an excessive amount causes a very active silicotic reaction, associated with necrosis. It appears probable that the absence of organisms in some of the silica lesions—for example, in three of six crystabolite and three of seven chalcedony foci—may have been due to the technical defects of the method.

In the case of the amorphous silicas, opal and diatomaceous earth, there is some uncertainty. Uncompleted experiments in the Saranac Laboratory show that both these substances are capable of producing necrosis and fibrosis of the viscera when injected into the ear veins of rabbits. Diatomite acts more rapidly than opal. The results in the subcutaneous experiment are rather surprising in that only one focus of diatomaceous earth was positive for bacilli, whereas five lesions from the less active opal contained demonstrable bacilli, and in two such lesions bacilli were more numerous than in the quartz controls. The evaluation of these results is best deferred until other observations have been completed.

TABLE 3.—*Estimated Number of Tubercle Bacilli in Single Lesions of Each Dust* *

	Mouse					
	1	2	3	4	5	6
Quartz	2	3	2	1	1	0
Crystabolite	0	0	1	1	1	0
Vitreous silica	1	4	1	1	1	1
Fluorspar, crude	0	5	0	1	0	0

	Mouse				
	7	8	9	10	11
Quartz	2	1	2	1	1
Tridymite	2	0	4	1	0
Feldspar	1	1	3	0	0
Carborundum	0	0	0	0	0

	Mouse					
	12	13	14	15	16	17
Quartz	1	1	1	1	1	1
Opal	0	0	0	3	1	1
Hematite	0	0	0	0	0	0
Garnet	0	0	0	0	0	0

	Mouse		
	18	19	20
Quartz	4	2	1
Diatomaceous earth	0	0	0
Granite	4	2	4
Chert	0	0	0

	Mouse			
	21	22	23	24
Quartz	1	1	2	1
Silica 20 A°	0	3	3	1
Chalcedony	0	3	3	0
Opal	0	1	3	0
Diatomaceous earth	0	0	3	0
Chert	0	0	0	0

	Mouse	
	25	26
Quartz	1	2
Sericite O	1	0
Sericite T	1	0
Sericite C	3	0

	Mouse		
	27	28	29
Quartz	2	2	4
Chalcedony	4	4	0
Talc	0	0	1
Sillimanite	0	0	1

	Mouse				
	30	31	32	33	34
Quartz	1	1	1	1	1
Synthetic zeolite	0	0	3	0	0
Glauconite	0	0	0	0	0

	Mouse			
	35	36	37	38
Quartz	2	1	4	3
Fluorspar, crude	3	1	1	2
Fluorspar, acid	2	0	0	1
Aluminum oxide	0	0	1	1

	Mouse											
	39	40	41	42	43	44	45	46	47	48	49	50
Quartz	3	1	1	1	2	1	1	2	1	4	1	3
Fluorspar, acid	2	2	0	1	2	1	0	2	0	0	1	1

* The estimated number is recorded as: scarce, 1; few, 2; numerous, 3; very numerous, 4.

When free silica was mixed with silicates in granite, all the lesions were positive, and bacilli were as numerous or more so than in the quartz controls. Clinical experience might lead one to suspect such a result. Crude fluorspar, which contains approximately 10 per cent free silica, yielded positive findings in six of ten injections. One lesion contained more bacilli than the control focus of pure crystalline silica. It was surprising to discover no organisms in the ferruginous chert foci, for approximately one half of the mineral is cryptocrystalline silica. The hematite likewise contains 6 per cent free silica in this form, and it produced no lesions in which bacilli could be detected. It is conceivable that the heavy brown dust obscured the acid-fast organisms. This is hardly likely, however, for bacilli were easily observed in stained smears of suspensions with high concentrations of these dusts.

In the case of the silicates the percentage of positive findings was variable. The fact that no bacilli were discovered in nodules produced by garnet and glauconite may be due to the masking color of these substances. On the other hand, some of the lesions from silicates showed as many organisms as the quartz control in the same animal; and in three foci, i.e., one each of feldspar, crude fluorspar and synthetic zeolite, the bacilli were more numerous. The asbestos minerals were not included in this study, as suitable specimens of the various varieties were not available at the time. They will be investigated in another connection. The small number of silicate lesions positive for bacilli (table 2) suggests that at least some of the combined forms of silica may have less capacity to stimulate growth of tubercle bacilli than free silica. But such a generalization cannot be made for all the silicates, for it will be seen in table 3 that the lesions caused by some of them contained more bacilli than the quartz controls. The inconsistencies suggest that the method is not altogether reliable and that conclusions are warranted only when large numbers of tests have been made on the same material.

The few nonsilicious dusts which were included furnished some surprises. Carborundum[16] has been shown to stimulate proliferation of R_1 tubercle bacilli in the lungs of guinea-pigs infected by inhalation, and yet not a single carborundum focus in the mice of this experiment contained visible organisms. No explanation is offered unless it be that the organisms were obscured by the color of the dust. Aluminum oxide, which in the artificial form is known as aloxite, is just as black. Its lesions were 50 per cent positive for organisms. Acid fluorspar, the trade designation for purified fluorspar, free from silica, gave lesions 62 per cent of which contained bacilli, and in many foci they were as numerous as in the quartz controls.

16. Gardner, L. U.: Am. Rev. Tuberc. **7**:344, 1923.

A comment might be made on the relationship between necrosis and the presence of bacilli in lesions of the various animals. Kettle[13] showed that necrosis per se is not the essential requirement by injecting other powerful irritants—turpentine, cantharidin and calcium chloride. This is borne out by the experiment under discussion. The injection of heavy suspensions of many of the silicas, such as silica 20 A°, crystabolite, tridymite, opal and diatomaceous earth, produced definite necrosis yet bacilli were not always found in the foci. The same may be said for eleven of the silicate lesions. For example, four of six reactions to garnet were necrotic, but all were negative for organisms. Of the lesions from mixed dusts, four of seven lesions from chert were necrotic, but none were positive for bacilli. Conversely, in the non-necrotic reactions to vitreous silica, the fluorspars and aluminum oxide the incidence of bacillary localization was higher than in those with necrosis. With the latter dust 50 per cent of the lesions were positive, yet none were necrotic.

These observations indicate that the method has its limitations and that when used to investigate the influence of mineral dusts other than pure silica it may lead to erroneous conclusions unless very large numbers of tests are made with each substance. The success of the method depends on the assumption that some of the organisms introduced into the circulation at a remote point will come to rest in the exact area where the dust particles have been injected. Since there is no evidence to indicate that a localized area of reaction to silica or other dusts exerts a chemotactic influence on the bacilli in the circulation, localization is more or less fortuitous. Injury of blood and lymph capillaries in the reaction to dust may also be a necessary concomitant, but probably this is sufficiently marked in the reaction to any of the dusts injected to permit the organisms to pass through the walls of the capillaries if they happen to be present within the vessels. Some of the inconsistencies in these results are therefore attributed to accidents of localization. Another source of error may have been the failure to select the proper area for section. Many of the dust foci were very small, and it was hard to be certain that even a series of sections included the necrotic center or the area richest in tubercle bacilli. Colored dusts like hematite, chert and carborundum may have obscured the organisms, although control examinations seemed to eliminate this possible source of error.

The second phase of the reaction depends on the amount of bacterial proliferation after the organisms reach the focus. Since there is no means of knowing how many tubercle bacilli were originally implanted in the area, it is difficult to evaluate the results on a quantitative basis. Kettle's fundamental observation that tubercle bacilli multiply rapidly in areas where free crystalline silica is reacting with

the tissue remains unchallenged. The few foci in which this was not observed were probably never infected because the organisms did not happen to reach them. The interval of time after infection is apparently important, as indicated by the failures in most of the animals in which it was as short as a week. The interval elapsing between the injection of the dust and the injection of the tubercle bacilli should be sufficient to permit maximal effects of the dust and allow complete healing of the trauma from the needle. Since the reactions to most of the dusts other than free silica were nonprogressive, it is felt that the age of the reaction to the dust was probably of little consequence.

SUMMARY

Subcutaneous injections of mineral dusts of different forms of silica in various concentrations and of nonsilicious dusts were made into the abdominal walls of white mice. The animals were infected with tubercle bacilli H_{63} injected intravenously and were put to death at different periods after infection. The character of the inflammatory response to each dust and the relative number of bacilli in each lesion were determined by microscopic examination.

On comparing the lesions produced by different dusts there was no evident relationship between the number of bacilli injected or the age of the reaction to the dust and the presence of tubercle bacilli in the focus. Necrosis was not a determining factor. The number of foci positive for bacilli could not be correlated with the amount of silica in the dust and its petrographic characteristics.

Group comparisons indicate that dust with a high content of free silica stimulates the growth of tubercle bacilli. Lesions produced by such dust were more often positive and contained more bacilli than those caused by silicate and nonsilicious dusts.

As a general proposition, Kettle's conclusion that bacilli tend to multiply in areas of reaction to pure crystalline silica has been verified. The converse conclusion that combined silica and nonsilicious dusts have no effect has not been confirmed.

For the method to be uniformly successful it is necessary that every dust focus contain at least one tubercle bacillus. The assumption that intravenous injection will distribute tubercle bacilli uniformly into all parts of the body is at least debatable. If a sufficient number of observations are made, it is probable that the capacities of different minerals to cause proliferation of tubercle bacilli can be ascertained. But single or even three or four tests are not sufficient for the purpose. Until some other method can be devised, this one remains the most feasible for rapid testing, but its limitations should always be kept in mind.

BOECK'S SARCOID

REPORT OF SIX CASES IN WHICH AUTOPSIES WERE MADE

D. A. NICKERSON, M.D.

BOSTON

Sarcoid is seldom fatal even when associated with visceral involvement and, consequently, pathologic descriptions of the findings are meager. It is the purpose of this paper to present the visceral manifestations in six clinically unrecognized cases of sarcoid seen during the past four years. In all but one of these cases death was due to some major disease, and the lesions of sarcoid were not recognized until the histologic sections were examined. In the one excepted, to be discussed later, atypical tuberculosis was diagnosed both clinically and at the time of autopsy, but the case is now believed to have been one of fatal sarcoid.

A historical review of the subject has been presented by Hunter [1] in a recent paper, to which the reader is referred.

There is abundant clinical evidence of systemic involvement associated with sarcoid of the skin. Among the lesions reported by various authors are: enlargement of the cervical, inguinal, mediastinal and mesenteric lymph nodes; infiltration of the lungs and upper air passages; splenomegaly; hepatomegaly; dactylitis with cystic changes in the phalanges; tonsillar swelling; iritis, and enlargement of the parotid gland.

A case with autopsy is decidedly rare. Bernstein, Konzelmann and Sidlick [2] in 1929 reported a case with clinical involvement of the skin and lungs in which autopsy showed lesions in the epicardium, bronchial mucous membrane and ileum.

A case of cutaneous sarcoid with typical histologic alterations in the brain was reported by Lenartowicz and Rothfeld [3] in 1930. In this case, however, there was coincident pulmonary miliary tuberculosis with fibrosis of the left lung, as well as tuberculosis of the abdominal organs and lymph nodes, a finding which casts some doubt on the validity of

From the Mallory Institute of Pathology, Boston City Hospital.

1. Hunter, F. T.: New England J. Med. **214**:346, 1936.

2. Bernstein, M.; Konzelmann, F. W., and Sidlick, D. M.: Arch. Int. Med. **44**:721, 1929.

3. Lenartowicz, J., and Rothfeld, J.: Arch. f. Dermat. u. Syph. **161**:504, 1930.

the lesions representing sarcoid. Mylius and Schürmann [4] reported two cases in 1930. In the first case lesions were present in the lung, lymph nodes, liver, fingers and toes. Again in this case there was coexistent pulmonary tuberculosis with calcification of mesenteric lymph nodes and caseation in a few of the phalangeal lesions. In the second case the autopsy was restricted to examination of the thoracic organs. The lesions of sarcoid were found in the lung and mediastinal lymph nodes, and there was no evidence of tuberculosis.

ETIOLOGY

Many theories have been advanced in an attempt to explain this condition. The most widely held opinion is that the disease is related to tuberculosis. Proof of this demands the finding of tubercle bacilli in stained sections or following inoculation in animals. In a great majority of the reported cases, however, the authors were unable to fulfil these requirements.

These negative results are usually interpreted as indicating the fact that the tubercle bacillus is of the bovine strain and that the tissue allergy of the patient is high as a result of a previous tuberculous infection.

Others substantiate their belief by quoting the work of Kyrle.[5] He believed that sarcoid was a foreign body type of response to the products of disintegration of the tubercle bacillus. He was able to study lesions of varying ages in a case of cutaneous sarcoid, and in a biopsy specimen of a lesion that had been present for ten days he found simple inflammation with many tubercle bacilli in the infiltrate. In lesions of three weeks' duration, many endothelial cells had appeared and the number of tubercle bacilli had diminished. After five weeks, no tubercle bacilli could be found, and the histologic picture corresponded with that of sarcoid. Wende [6] in 1910 also claimed to have found tubercle bacilli in early lesions.

Goeckerman [7] stressed the finding of tubercle bacilli in the early lesions and believed that a greater number of positive results would be obtained in stained sections and following inoculation in animals if early lesions were removed instead of the older classic ones.

Pautrier and Glasser [8] in 1936, in reporting a case of sarcoid of the skin, claimed to have produced a lesion at the site of inoculation in

4. Mylius, K., and Schürmann, P.: Beitr. z. Klin. d. Tuberk. **73**:166, 1930.

5. Kyrle, J.: Vorlesungen über Histo-Biologie der menschlichen Haut und ihrer Erkrankungen, Berlin, Julius Springer, 1927, vol. 2, pp. 207-211.

6. Wende, G. W.: J. Cutan. Dis. **29**:1, 1911.

7. Goeckerman, W. H.: Arch. Dermat. & Syph. **18**:237, 1928.

8. Pautrier, L. M., and Glasser, R.: Bull. Soc. franç. de dermat. et syph. **43**:505, 1936.

one of two rabbits and to have demonstrated acid-fast bacilli, presumably of the bovine type, in the lesion. However, they stated that the original skin lesion had "a structure more tuberculous than usual."

In opposition to this theory of tuberculous origin is the common belief that the disease with organic involvement is a benign disease of middle life, with many of the cases being recognized during the third and fourth decades. The condition runs a chronic course with perhaps spontaneous remissions, and the patient dies of some major disease. This clinical course and the fact that no evidence of tuberculosis can be found grossly, microscopically or following inoculation in animals suggest some other etiologic agent.

Kuznitsky and Bittorf [9] were the first to suggest that sarcoid represents a disease sui generis. Rischin [10] and Whittemore [11] later came to the same conclusion, and the latter reported a case in which he established that sepsis was the cause. Kissmeyer,[12] in agreeing that sarcoid is a disease entity, postulated first that it might be a virus infection. In accord with this theory, an antigen has been prepared from cutaneous lesions which evokes specific skin reactions as reported in a previous paper.[13]

Another theory favored by many French authors is that the lesions of sarcoid represent a nonspecific reaction in a "terrain sarcoïdique" in response to infections of various types or to injections of foreign substances. Maloney and Combes [14] came to the same conclusion.

Syphilis has been stressed by Frazier and Hu [15] and Pautrier.[16] These authors reported cases of cutaneous sarcoid in patients with positive Wassermann reactions, with disappearance of the lesions under antisyphilitic treatment. The majority of reported cases, however, are characterized by negative serologic observations.

MATERIAL

In this laboratory during the past four years the lesions of sarcoid were found in six cases in which autopsies were made. This study is based on these cases. The table gives the location of the lesions.

9. Kuznitsky, E., and Bittorf, A.: München. med. Wchnschr. **62**:1349, 1915.
10. Rischin, M.: Arch. f. Dermat. u. Syph. **139**:30, 1922.
11. Whittemore, E. R.: Arch. Dermat. & Syph. **11**:56, 1925.
12. Kissmeyer, A.: La maladie de Boeck: Sarcoides cutanées bénignes multiples, Copenhagen, Levin & Munksgaard, 1932.
13. Williams, R. H., and Nickerson, D. A.: Proc. Soc. Exper. Biol. & Med. **33**:404, 1935.
14. Maloney, E. R., and Combes, F. C.: Arch. Dermat. & Syph. **33**:709, 1936.
15. Frazier, C. N., and Hu, C. K.: Proc. Soc. Exper. Biol. & Med. **30**:898, 1933.
16. Pautrier, L. M.: Ann. de dermat. et syph. **5**:344, 1914-1915.

SUMMARY OF THE PATHOLOGIC OBSERVATIONS

Gross Observations.—In only one case (table, no. 1) were the gross findings unusual. The patient, a middle-aged Negress, undoubtedly had an acute, overwhelming sarcoid infection. She had been in this hospital six months before death, at which time a mass was removed from the eyelid. The pathologic diagnosis at that time was atypical tuberculosis of the eyelid with involvement of the lacrimal gland. No caseation was present in the lesion, and special stains for tubercle bacilli were negative. On the last entry, the patient was markedly dyspneic, and the respirations were wheezing in nature. Physical examination showed signs of impairment of the entire right lung, with diminished breath sounds. The heart was enlarged transversely. The sounds were regular but rapid and weak. No murmurs were heard. No cutaneous lesions were noted on either admission. The patient grew gradually weaker during her stay in the hospital and

Distribution of Lesions

Case	1	2	3	4	5	6
Age	58	67	43	53	45	62
Sex	F	M	M	F	M	F
Heart	+	0	0	0	0	0
Lung	+	0	0	+	+	+
Spleen	+	+	+	+	0	+
Liver	+	+	0	+	+	+
Pancreas	0	0	0	+	0	0
Kidney	0	0	0	0	0	0
Adrenal gland	—	0	—	0	0	0
Testis	—	+	0	—	0	0
Lymph nodes	+	—	—	+	—	+
Bone marrow						
Vertebral	—	+	+	0	0	+
Femoral	—	—	—	+	—	—
Tibial	—	—	—	0	—	—
Brain	—	—	—	0	0	—
Pituitary gland	—	—	—	0	0	—
Skin	—	0	—	—	—	—
Eyelid	+	—	—	—	—	—
Cause of death	? Sarcoid	Cardiac decompensation, bronchopneumonia	Lobar pneumonia	Cerebellar hemorrhage	Rupture of aneurysm of midcerebral artery	Lobar pneumonia

+, lesions were present; 0, lesions were absent; —, tissue was not available.

died eighty-three days after admission. The clinical diagnosis was atypical tuberculosis of the lungs and lymph nodes and bronchial asthma. The striking gross lesion consisted of numerous small flat firm white nodules from 1 to 4 mm. in diameter scattered over the parietal pleura of the right lung posteriorly and the parietal pericardium. These nodules had coalesced to form irregular plaques of homogeneous granular pale white tissue, from 0.3 to 1.5 cm. in diameter, in both the pleura and the pericardium. The pericardial cavity contained 150 cc. of clear amber fluid. The other findings are given in subsequent paragraphs relating to the various organs.

In the other cases there were no outstanding gross findings except the major disease causing death. The most constant feature was unexplained splenomegaly with or without abdominal lymphadenopathy.

The spleens in four cases were enlarged, weighing 200, 230, 640 and 890 Gm., respectively. Their external surfaces were smooth and glistening. The two largest spleens cut with definitely increased resistance to reveal pale pinkish gray surfaces, which were firm and dry and almost completely replaced by great numbers of pale

gray nodules from 1 to 3 mm. in diameter. The normal architecture was obscured, and no scrapings could be obtained. The other spleens cut with normal resistance to reveal moist reddish gray surfaces, over which were scattered moderate numbers of similar nodules. The normal markings were present and a moderate amount of pulp scraped.

In two cases, the mesenteric, retro-aortic, gastrohepatic and tracheobronchial nodes were enlarged up to 3 cm. in diameter. On section they were gray, firm and finely granular.

The livers in four cases were enlarged and weighed from 1,700 to 3,100 Gm. The largest one showed definite evidence of cirrhosis, and the other three were grossly normal.

Gross examination of the pancreas, kidneys, adrenal glands, genital organs, bone marrow and brain in each case disclosed nothing remarkable. Lesions of the skin were not observed.

Microscopic Observations.—The microscopic observations were confined to lesions of the type first described by Boeck.[17] They were present in varying numbers in the organs as listed here and were most numerous in the spleen and lymph nodes.

The lesions were well defined single or confluent round inflammatory lesions, consisting of fibrous tissue, infiltrated by moderate numbers of elliptic macrophages and a few lymphocytes. About the periphery were fairly numerous lymphocytes and occasional macrophages and eosinophilic polymorphonuclear leukocytes. Many of the lesions contained multinucleated giant cells. No areas of caseation were present, and only a rare neutrophilic polymorphonuclear leukocyte was noted. In the centers of a few of the nodules in one case were small amounts of fibrinoid material. When the lesions were sparse, they remained solitary; when numerous, they often coalesced to form conglomerate masses.

About these nodules, particularly in the spleen and lymph nodes, there were wavy bundles of homogeneous eosinophilic material. This material, while constant in the individual case, varied with each case. With silver impregnation, this was shown to be collagen, which appeared to result from condensation of reticulum about each nodule. This stain also showed the presence of a delicate network of reticulum in each nodule. In cases in which the condition was proved to be tuberculosis there was a similar distribution of collagen about the periphery of each tubercle, but, as was shown by Medlar,[18] when caseation occurred, the network of reticulum within the tubercle was destroyed.

Only a small amount of collagen was present in the case in which death was due to a sarcoid infection. In the other cases, in which the lesions of sarcoid were incidental findings, a relatively large amount was present between the lesions and often within them. Most of the cells had disappeared, leaving only the elliptic macrophages and the giant cells.

No evidence of tuberculosis was found in any of these cases either grossly or microscopically. Ziehl-Neelsen stains were repeatedly negative. No inoculations were made in animals. Surgical material showing a similar histologic picture gave uniformly negative results following inoculation into a series of animals.

Examination of sections from each case for singly or doubly refractile bodies gave negative results in every instance. A spiculated body was found in a giant cell in a section of the lung in one case.

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17. Boeck, C.: J. Cutan. & Genito-Urin. Dis. **17**:543, 1899.
18. Medlar, E. M.: Am. J. Path. **2**:275, 1926.

The distribution of the microscopic lesions was as follows:

Heart: Lesions were present in the heart in only one case. They were few and solitary and were found in the myocardium, perivascular fibrous tissue and subendocardial fibrous tissue.

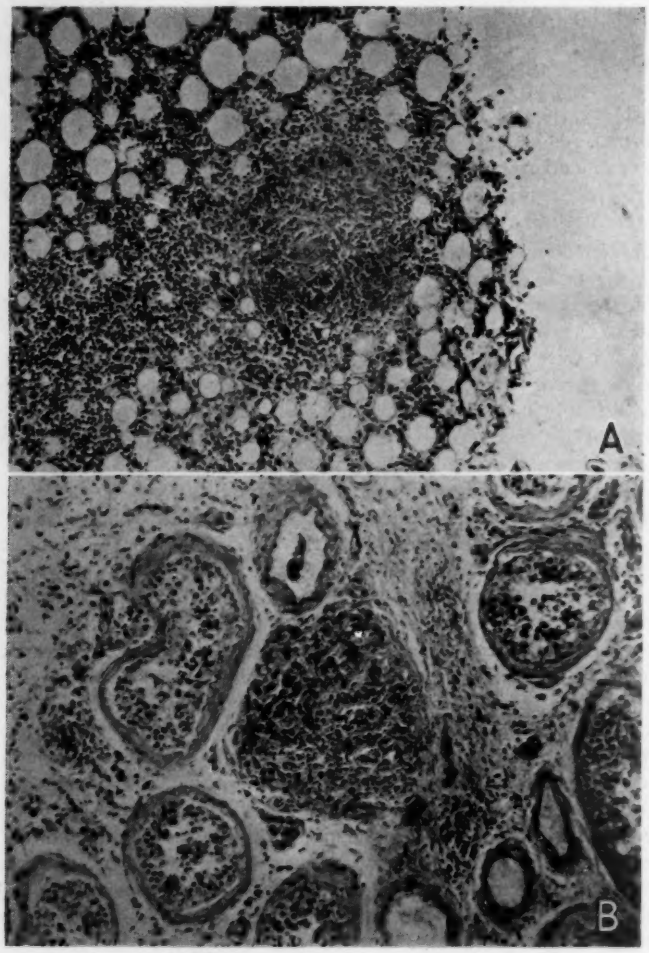

Fig. 1.—*A*, solitary lesion in the femoral marrow; reduced from ×93. *B*, solitary lesion in the interstitial tissue of the testis; reduced from ×93. The tissues shown in this and subsequent illustrations were fixed in Zenker's fluid, and sections were stained with phloxine-methylene blue.

Lung: Lesions were present in the lungs in four cases. They occurred in moderate numbers, and some were solitary and some confluent. In each case, they were found in three distinct areas: (1) pleural, often forming confluent masses in the subpleural fibrous tissue; (2) peribronchial, occurring usually as solitary

lesions which tended to encircle the smaller bronchioles, and (3) septal, occurring commonly as solitary lesions in the alveolar septums.

It has been suggested from roentgenologic studies of the lungs that the disease extends peripherally through the lymphatic vessels. In these cases no relation to lymphatic or to blood vessels was apparent.

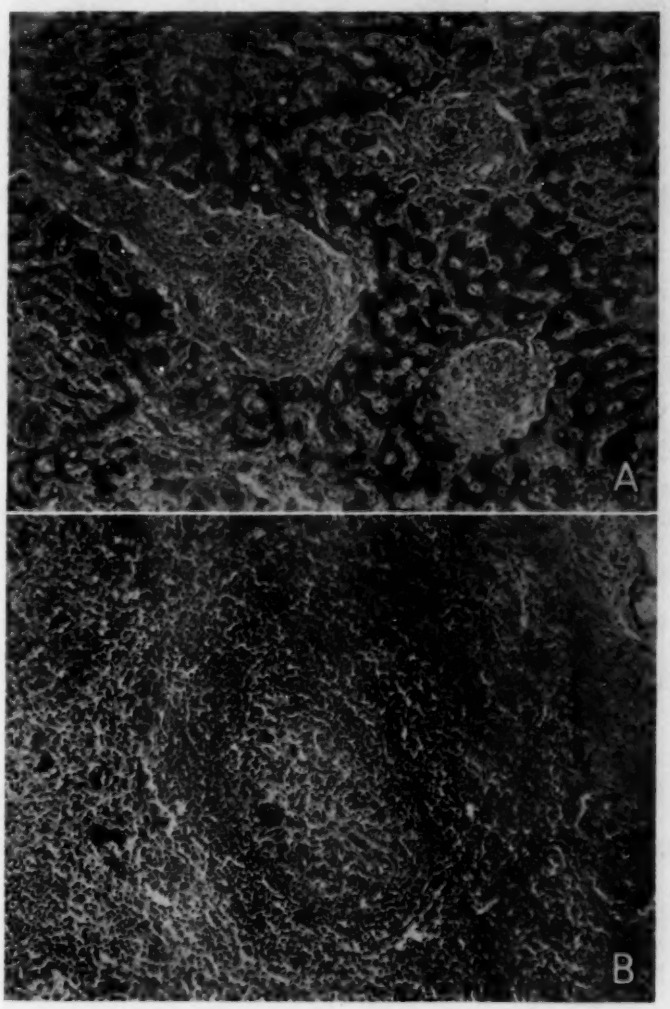

Fig. 2.—*A*, lesions confined to the portal areas of the liver; reduced from ×93. *B*, lesion in the germinal center of a malpighian corpuscle of the spleen; reduced from ×93.

Spleen: Lesions were found in all but one spleen. In the two largest spleens they were so numerous as to replace almost completely the parenchyma and were predominantly of the large, conglomerate type. The lesions appeared to have a

predilection for lymphoid tissue, and no germinal centers remained uninvolved. Numerous giant cells were noted, and only a moderate amount of collagen was present.

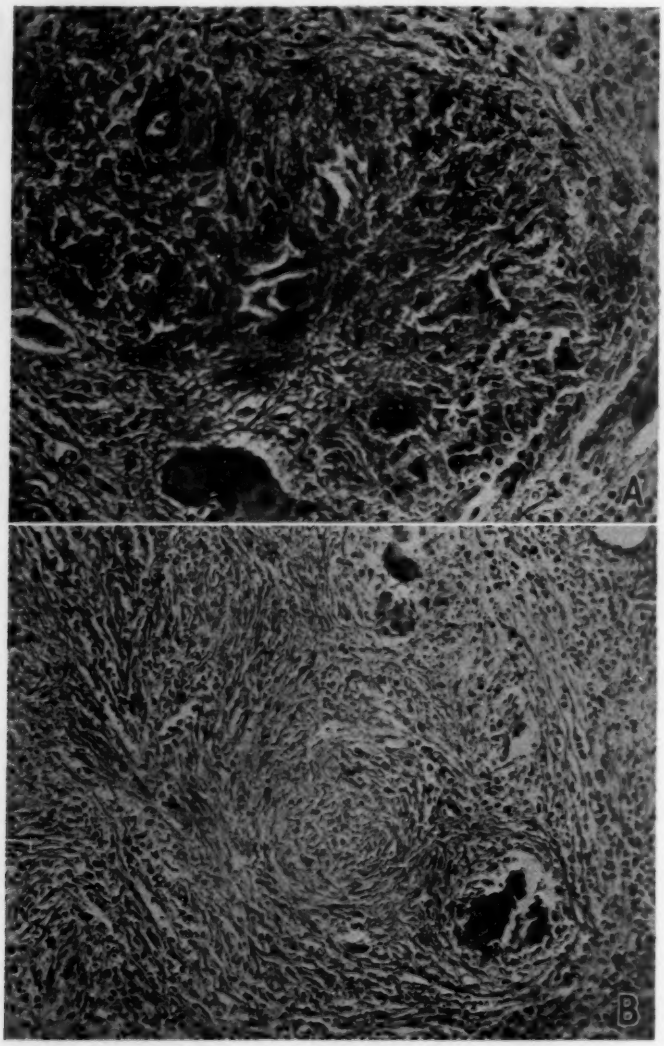

Fig. 3.—*A*, acute lesion in the liver; reduced from × 226. A small amount of fibrinoid material is present in the center of the lesion. Caseation and leukocytic infiltration are absent. *B*, healed lesion in a lymph node, showing replacement by a large amount of collagen; reduced from × 226. Giant cells are still present.

In the other spleens, the lesions were moderately numerous and solitary. They were found only in the lymphoid tissue of the germinal follicles. No other significant changes were noted.

Pancreas: In only one case were lesions present in the pancreas. They were relatively rare and solitary and were found in the interacinous and intra-acinous fibrous tissue. There was no involvement of the acini or of the islets.

Liver: Lesions were present in the liver in all but one case. They were moderately numerous and usually solitary and occurred in greatest numbers in the portal fibrous tissue but were also sometimes found in the lobules in a midzonal position.

Testis: There were four males in this series, only one of whom had testicular lesions. The lesions were few and always solitary and occurred only in the interstitial tissue. The seminiferous tubules appeared normal, and there was normal spermatogenesis.

Lymph Nodes: Lymph nodes were removed in only three cases. Lesions were present in all. They were very numerous and usually confluent and almost completely replaced the parenchyma in every case, leaving only a thin rim of lymphoid tissue beneath the capsule. The lymph nodes contained the largest amount of collagen seen in any case. It is of interest that a minimal amount of this material was observed in the lymph nodes from the patient in whom death was due to a sarcoid infection.

Bone Marrow: Bone marrow was available in five cases. Lesions were found in the vertebral marrow in three. They were sparse but usually conglomerate and were found in the midst of a mass of hematopoietic tissue. A dense rim of lymphocytes and eosinophilic polymorphonuclear leukocytes surrounded each lesion. A minimal amount of collagen was present.

In the one case in which the femoral marrow was examined, a few solitary lesions were present, scattered in groups of fat cells in an inactive marrow. No lesions were noted in an inactive tibial marrow in this case.

Skin: Unfortunately, sections of the skin were removed in only one case, and these were taken from the temporal region in a case known to be one of basal cell carcinoma. No sarcoid lesions were present.

Lacrimal Gland: As has been stated before, lesions were found in the eyelid with involvement of the lacrimal gland in a biopsy specimen taken from the first case six months before death.

Other Organs: No lesions were present in the kidney, adrenal glands, cerebrum, cerebellum or pituitary gland in any case. Permission to examine the brain was obtained in only two cases.

COMMENT

This series of cases is apparently the first in which lesions have been reported in the myocardium, endocardium, pancreas, testis and vertebral and femoral marrow. It is of interest that lesions were found in the spleen in five cases, with definite splenomegaly in four, and in the lungs in four cases, as these are the most common clinical sites. It is particularly unfortunate that sections of skin were not available in each case.

In studying these cases several important questions arise. The first is: What histologic criteria are necessary to make the diagnosis of sarcoid and to differentiate it from tuberculosis?

The aforementioned microscopic picture has been adopted as typical of the condition. In differentiating sarcoid from tuberculosis, especially the miliary form, the following findings are of assistance:

1. Caseation should never be present. The one case in this series in which a few of the lesions contained small amounts of fibrinoid material is to be regarded as an example of the acute fulminating form of the disease. In none of the lesions of sarcoid are any neutrophilic polymorphonuclear leukocytes seen, a finding one would expect in an early caseating tubercle.

2. The giant cells are different from those seen in tuberculosis. They show moderate variation in size, are usually much larger and contain many more nuclei (often as many as from 25 to 30), which are evenly distributed throughout the cell and are seldom arranged in the elliptic manner typical of tuberculous giant cells.

3. Lesions in tissues other than the lungs do not contain carbon pigment.

4. In the liver the lesions are most numerous in the portal triads, with only a few in the midzones of the lobules. In miliary tuberculosis the reverse is true.

5. With silver impregnation, a delicate reticulum is always present in the lesion. In tuberculosis this is destroyed by the onset of caseation.

6. No evidence of tuberculosis is found anywhere in the body.

Many authors believe that giant cells should never be present in the older, quiescent lesions, as they assume that their presence denotes activity of the infection. It appears from this study that giant cells may occur in all stages of the disease.

The amount of collagen present seems to be a more accurate index of the activity of the infection. In the only case in which a minimal amount was present between the lesions, death was apparently due to this disease. In all other cases a much greater amount was present between, and often in, the individual lesions. It is felt, therefore, that the presence of increased amounts of collagen indicates a healing reaction.

The other important question is the relation of sarcoid-like lesions to the true lesions of sarcoid as seen in this series. In the surgical material in this laboratory, sarcoid-like lesions have often been found in Hodgkin's disease, have been noted in the midst of tumor cells in a cancer of the breast and have also been seen in the retro-aortic lymph nodes in a patient who died of cancer of the stomach. Sarcoid-like lesions have also been reported by various authors in patients with syphilis, leprosy and traumatic necrosis of fat and in the new-born.

Histologically, the sarcoid-like lesions are composed of small irregular foci of elliptic macrophages with occasional areas of fibrosis and rare giant cells or lymphocytic infiltration. These lesions may be differentiated from true sarcoid, as they lack the smooth outline and cellular infiltration of the latter. While they may thus be distinguished, their significance and possible relationship are not yet entirely clear.

SUMMARY

Six cases are presented in which autopsies were made and the typical histologic picture of sarcoid found in the viscera.

In one instance, the patient undoubtedly died of sarcoid in a fulminating form. The other cases are examples of incidental sarcoid, the patients dying of some major disease.

Lesions are reported in the myocardium, endocardium, pancreas, testis and vertebral and femoral marrow for the first time.

A varying amount of collagen was noted in each case. It was minimal in the case in which death was apparently due to the disease, and it is suggested that an increase in the amount of collagen indicates a healing reaction.

HYPERPLASIA OF THE PARATHYROID GLANDS SECONDARY TO RENAL INSUFFICIENCY

REPORT OF A CASE

ARTHUR A. NELSON, M.D.
MINNEAPOLIS

Hyperplasia of the parathyroid glands secondary to renal insufficiency is to be distinguished from primary hyperparathyroidism with secondary renal insufficiency from deposition of calcium in the kidneys. About twenty cases of such hyperplasia of the parathyroid glands have now been reported. These were reviewed by Magnus and Scott [1] in 1936, who reported a case of their own and summarized the seven individual cases and Bergstrand's [2] series of ten cases previously reported. They also included Pappenheimer and Wilens' [3] group of twenty-one cases with severe renal insufficiency, in which the average combined weight of the parathyroid glands was double the normal. Not listed by Magnus and Scott are a case observed at the Massachusetts General Hospital [4] and one reported by Kluge.[5] In only one of the aforementioned cases [6] was the renal insufficiency caused by congenital polycystic kidneys, and for this reason a second case is now reported.

A white woman 47 years of age was admitted to the hospital, May 19, 1935, with a neoplastic mass in the abdomen of at least one year's duration, weakness and a 40 pound (18 Kg.) loss in weight. There had also been occasional nausea and vomiting, with three or four stools per day without pus, blood or mucus. The patient had been under treatment for high blood pressure for ten years, but there was no record of the blood pressure. One brother died in 1933 of renal insufficiency from congenital polycystic kidneys. Five children were living and well.

The entire left side of the abdomen was filled by a fixed irregular mass that was somewhat tender. In the region of the right kidney was a nontender smaller mass. The rest of the physical examination showed essentially normal conditions.

From the Department of Pathology and the Cancer Institute, University of Minnesota.

1. Magnus, H. A., and Scott, R. B.: J. Path. & Bact. **42**:665, 1936.
2. Bergstrand, H.: Acta med. Scandinav. **54**:539, 1921.
3. Pappenheimer, A. M., and Wilens, S. L.: Am. J. Path. **11**:73, 1935.
4. Cabot Case 22072, New England J. Med. **214**:317, 1936.
5. Kluge, E.: Virchows Arch. f. path. Anat. **298**:406, 1936 (case 4).
6. Gutman, A. B.; Swenson, P. C., and Parsons, W. B.: J. A. M. A. **103**: 87, 1934.

The hemoglobin was 46 per cent; the red cells were 2,630,000, and the white blood cells 3,850, per cubic millimeter, with 78 per cent neutrophils. The Wassermann test was negative. Urinalysis showed a specific gravity of 1.010, albumin (+ 1) and no sugar.

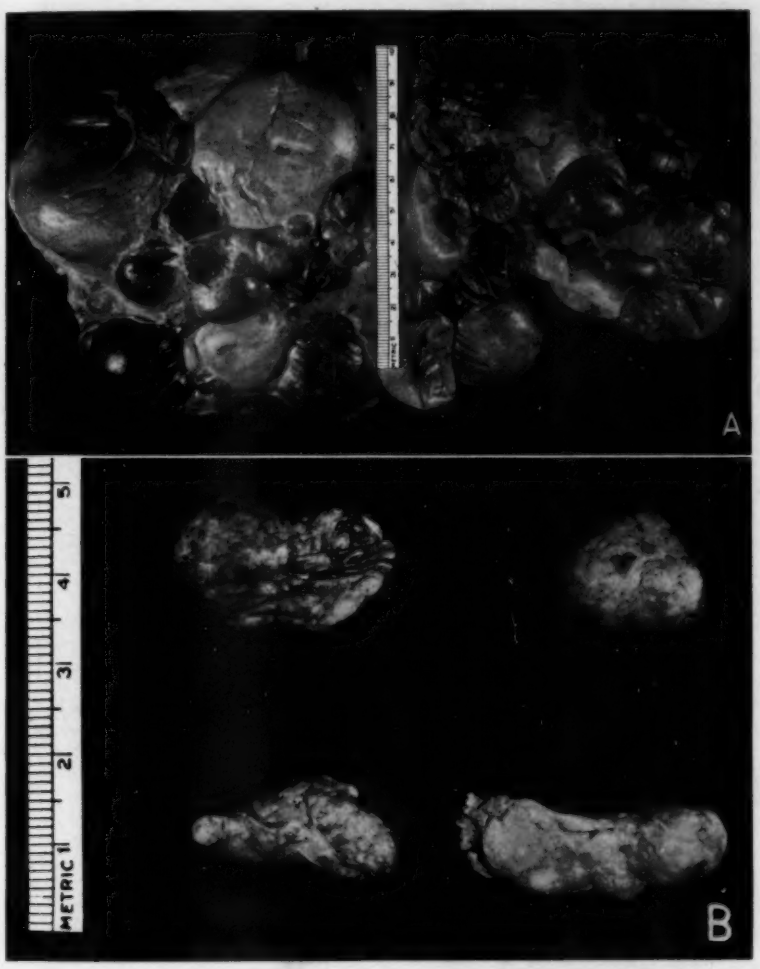

Fig. 1.—*A*, view of the external surface of one of the polycystic kidneys. The darker cysts are filled with bloody fluid; the lighter ones, with clear fluid. Practically no normal renal tissue can be seen. *B*, parathyroid glands from the patient with polycystic kidneys.

Roentgen examination disclosed a deformity of the stomach and duodenum caused by a large abdominal mass. An attempt to make an intravenous pyelogram was unsuccessful; no contrast material appeared in the pelves of the kidneys in

one hour. A retrograde pyelogram showed elongation and pressure deformation of the pelves, more marked on the left, and was considered characteristic of marked polycystic disease of the kidneys. No changes in bones were mentioned.

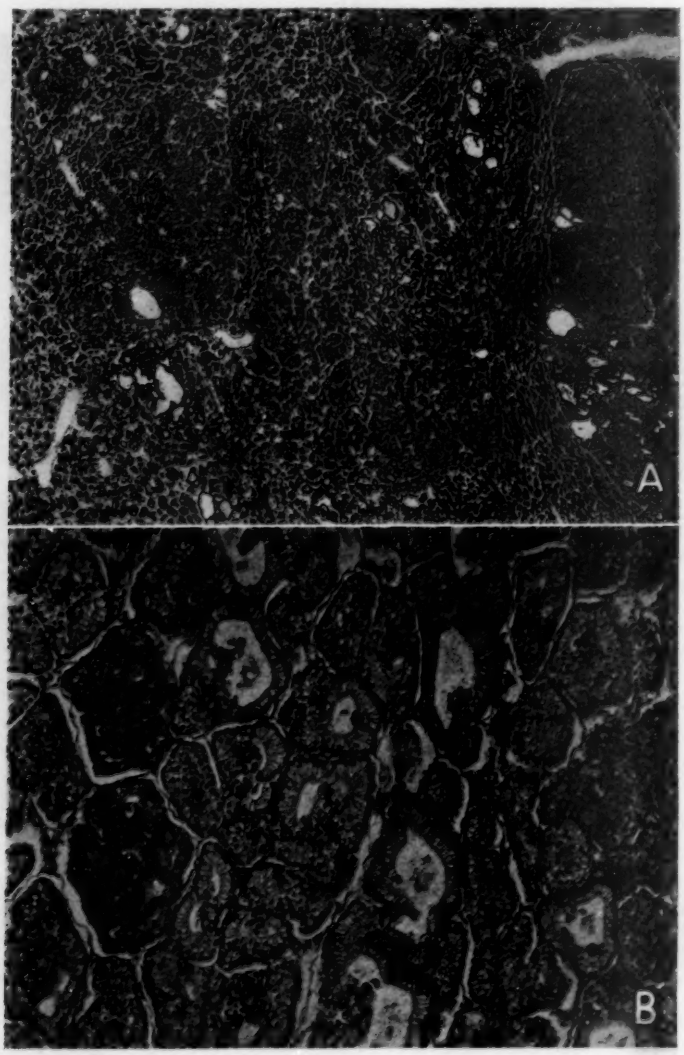

Fig. 2.—*A*, section from the left lower parathyroid gland (low magnification). Rounded compact masses of oxyphil cells can be seen, with chief cells in glandular formations between them. *B*, glandular formations of chief cells in the right upper parathyroid gland (high magnification).

Cystoscopic examination showed the urethra and bladder normal. Urine drained freely from both ureters and contained no pus or bacteria. Intravenously injected indigo carmine appeared first on the right side, at fifteen minutes.

The clinical diagnosis was polycystic kidneys. The patient was sent home, May 25, 1935, where she remained in bed and became progressively weaker. Large ulcers appeared on the skin of the legs. Death occurred June 17, 1936.

Autopsy.—The body was moderately emaciated. There were large ulcers over the lower halves of both legs, also large purpuric areas over the thighs. The lungs showed nothing of note.

The heart weighed 300 Gm. There were several small areas of myocardial fibrosis, a moderate amount of coronary sclerosis and a calcified area 5 mm. in diameter in the myocardium under the posterior cusp of the mitral valve.

The spleen weighed 305 Gm. It showed several red infarcts up to 2.5 cm. in diameter, and there was very marked medial calcification of the splenic artery.

The liver weighed 2,300 Gm. It contained several dozen cysts, one 8 cm. in diameter, the rest 3 cm. or less; the parenchyma showed nothing of note.

The gallbladder measured 5 by 14 cm. It contained about twenty-five polyhedral stones measuring up to 1.5 cm.; the main hepatic, cystic and common ducts together contained another twenty-five stones measuring up to 7 mm. in diameter. The gallbladder and ducts contained bile.

Of the kidneys, the right measured 30 by 14 by 9 cm. and weighed 1,550 Gm., while the left measured 29 by 18 by 12 cm. and weighed 2,250 Gm. The kidneys (fig. 1 *A*) were composed of large and small cysts, some filled with clear fluid, some with cloudy material and some with blood. Practically no normal renal tissue was recognizable. The ureters and bladder were normal.

The aorta showed moderate atherosclerosis with calcification.

The parathyroids (fig. 1 *B*) had the following dimensions and weights: upper right, 23 by 13 by 7 mm. (850 mg.); upper left, 25 by 16 by 9 mm. (1,675 mg.); lower right, 31 by 11 by 6 mm. (1,150 mg.); lower left, 17 by 16 by 7 mm. (750 mg.); total weight, 4,425 mg. On section, numerous small adenoma-like areas could be seen, also one area of hemorrhage 5 mm. in diameter. Otherwise the glands were of uniform soft consistency. The thyroid gland was normal.

The ribs and spine showed no apparent decrease of calcium.

Microscopic Observations.—All four parathyroids showed essentially hyperplasia of the chief and oxyphil cells. About 75 per cent of the cells were chief cells; the rest were oxyphil cells, with some transitional forms. There were no *wasserhelle* cells and practically no transitional *wasserhelle* cells. The oxyphil cells showed a marked tendency to form rounded masses (fig. 2 *A*); the chief cells were often in glandular formations (fig. 2 *B*). There were a few cysts up to 1 mm. in diameter.

The kidneys showed islands of compressed renal parenchyma between the cysts. These areas showed normal glomeruli and atrophic dilated tubules. There was a small amount of calcium in the tubules.

In the left tibia (upper end), in places, there was a slight degree of resorption of bone by osteoclasts. The spaces between the bony trabeculae were filled with fatty marrow.

In a lumbar vertebra, about one half of the trabeculae showed a slight degree of resorption and were becoming surrounded by loose fibrous tissue. By far the greater portion of the vertebra, however, was still filled with normal compact red bone marrow. The change was suggestive of early osteitis fibrosa.

COMMENT

This is the second case of parathyroid hyperplasia reported in association with polycystic kidneys. Bergstrand [2] and Pappenheimer and Wilens [3] either did not have or did not mention polycystic kidneys in their series of cases of renal insufficiency. Kurokawa's [7] series of 240 autopsies in which the parathyroids were examined included no cases of polycystic kidneys.

The fact that Bergstrand found ten cases of marked parathyroid hyperplasia in a series of fifty cases of nephritis indicates that the association of parathyroid hyperplasia and renal insufficiency occurs too frequently to be mere coincidence. The cellular picture in cases of parathyroid hyperplasia secondary to renal insufficiency shows no uniformity. Some reports show the glands to be composed mainly of chief cells, others of *wasserhelle* cells, and others of various mixtures and transitional forms.

For a discussion of the mechanism of parathyroid hyperplasia in renal insufficiency, the reader is referred to the monograph on the parathyroid glands by Shelling.[8] The pathogenesis of the hyperplasia is uncertain.

The causes of secondary parathyroid hyperplasia other than renal insufficiency are also reviewed by Shelling. The cases in which the condition follows rickets and osteomalacia appear to be the most definite. One case in which there was marked hyperplasia of one gland and in which the bones were involved by metastatic carcinoma was reported by Klemperer.[9] Parathyroid hyperplasia has also been reported with acromegaly.[10]

I may briefly mention here a second case of parathyroid hyperplasia which showed that factors other than renal insufficiency are capable of causing diffuse hyperplasia. At autopsy on a woman 73 years of age with multiple intestinal obstructions from metastases of a carcinoma of the gallbladder, all four parathyroids were enlarged and weighed 910 mg. together, six or seven times the normal weight. Microscopically, all four glands showed only *wasserhelle* and transitional *wasserhelle* cells. The kidneys grossly and microscopically showed no disease. The ribs and vertebrae grossly and microscopically appeared normal.

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7. Kurokawa, K.: Japan M. World **5**:241, 1925.

8. Shelling, D. H.: The Parathyroids in Health and Disease, St. Louis, C. V. Mosby Company, 1935.

9. Klemperer, P.: Surg., Gynec. & Obst. **36**:11, 1923.

10. Cushing, H., and Davidoff, L.: Pathological Findings in Four Autopsied Cases of Acromegaly with a Discussion of Their Significance, Monograph 22, Rockefeller Institute for Medical Research, 1927.

SUMMARY

About twenty cases of marked hyperplasia of the parathyroid glands in association with renal insufficiency have been reported in the literature. There is reported here the second case of such hyperplasia found in association with congenital polycystic kidneys. Brief mention is also made of another case of parathyroid hyperplasia in which there was neither renal insufficiency nor changes in the bones.

TALCUM POWDER GRANULOMA

ROBERT FIENBERG, M.D.
BOSTON

Only one article dealing with talcum powder granuloma could be found in the literature. This was an article by Antopol,[1] devoted mainly to lycopodium granuloma. A short description of one case was given, in which a foreign body reaction was found in the presence of anisotropic crystals which morphologically resembled talc crystals (magnesium silicate—3 $MgO.4SiO_2.H_2O$).[1a]

My interest was aroused by a patient who entered the hospital with a diagnosis of tumor of the abdominal wall.

REPORT OF CASES

CASE 1.—A 44 year old woman had had an appendectomy and a herniorrhaphy in another hospital seven years prior to examination in the present instance. Six years later she had a slightly tender mass in the region of the old appendectomy scar. There was no diarrhea, constipation or loss in weight. Examination showed a small firm mass at the upper end of the scar, apparently in the subcutaneous tissues.

An exploratory laparotomy was made, with excision of the scar. It was observed that an unusual gray translucent nodular tissue occupied much of the fascia. On account of this extensive infiltration, the abdomen was opened. Over the entire cecum were slightly raised grayish translucent nodular plaques. In the omentum were several small translucent nodules and a generalized scattering of thin translucent granular tissue. Enlarged firm lymph nodes lay above the stomach in the preaortic region. On the lateral wall of the gallbladder were three small grayish translucent nodules. The appendix was absent. The scar in the abdominal wall was excised, with section of the anterior fascia, rectus muscle and peritoneum about the tumor.

The patient was discharged shortly before this paper was written, so that the ultimate course is unknown.

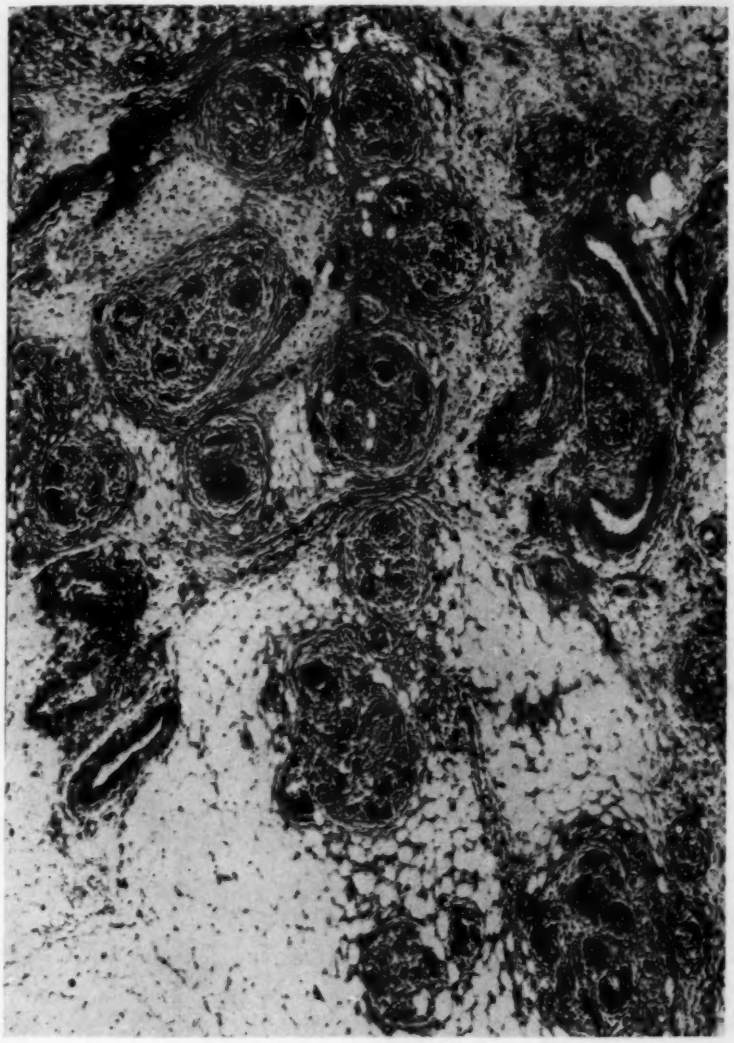
The specimen consisted of a piece of skin, subcutaneous fat and muscle, 12 by 6 by 3 cm. The skin measured 9.5 by 3.5 cm. and contained a scar 7 cm. long. The tissue between the muscle and the subcutaneous fat was dense, gray and translucent, with opaque grayish white trabeculae. This tissue extended into the subcutaneous fat and corium in an irregularly radiating manner. Also, there was a piece of muscle and connective tissue, 6.5 by 3 by 1.5 cm. The connective tissue was firm, translucent, slightly granular and pinkish gray.

From the Laboratory of Pathology, New England Deaconess Hospital.

1. Antopol, W.: Arch. Path. **16**:326, 1933.

1a. Recently a case of glove powder granuloma has been described (Owen, M.: Texas State J. Med. **32**:482, 1936).

Microscopic Examination.—Sections were prepared with eosin-methylene blue stain. An extensive lesion was seen, consisting of dense hyaline connective tissue in which numerous pseudotubercles were present. The lesion involved the



Talcum powder granuloma (case 1); eosin-methylene blue stain; × 48. Pseudotubercles containing numerous multinucleated foreign body giant cells invade the subcutaneous fat of the abdominal wall.

corium, subcutaneous fat and muscle. The more well defined nodules consisted of rounded collections of fibroblasts and endothelial cells with numerous large foreign body giant cells. In addition, lymphocytes were noted within the pseudotubercles, as well as a few infrequent polymorphonuclear leukocytes. Flattened,

elongated fibroblasts occurred at the periphery. Here and there one or two giant cells were present, surrounded in some instances by a few endothelial cells. The giant cells contained numerous oval nuclei with small chromatin masses. These nuclei were at times arranged in a semicircle at the periphery and at other times were scattered throughout the cell. The cytoplasm of the giant cells was abundant, and often small spaces were visible within it, apparently containing crystals. In some regions coalescence of the nodules had occurred.

Under crossed Nicol prisms, numerous anisotropic crystals were visible within the giant cells.

The diagnosis was a foreign body reaction.

Case 2.—A 67 year old woman five years previously had been given a diagnosis of primary hyperthyroidism, and had a subtotal thyroidectomy in two stages. The pathologic diagnosis was primary hyperplasia of the thyroid gland with moderate involution. In the present instance she was admitted for a swelling which had been present in the region of the thyroid gland during the past three years. The left lobe of the gland was easily felt; the isthmus was partly substernal. There was no evidence of hyperthyroidism. The basal metabolic rate was + 4. It was felt that the remnants of the thyroid gland were a potential source of trouble and should be removed.

An excision of the thyroid remnants was made. Following the operation, the basal metabolic rate was + 11.

The specimen consisted of four irregular firm scraps of thyroid tissue, the total weight of which was 20 Gm. A small amount of muscle was attached. There was much increase in fibrous tissue. The thyroid tissue was translucent and pink.

Microscopic Examination.—The sections were prepared with the hematoxylin and eosin stain. An extensive lesion was seen, consisting of fibrosis and well developed pseudotubercles. Material staining with hematoxylin was present about some collections of crystals within giant cells.

Under crossed Nicol prisms, numerous anisotropic crystals were found within the giant cells.

The diagnosis was primary hyperplasia with late involution and hyperinvolution, recurrent, and a foreign body reaction.

A mineralogical analysis revealed that the crystals in the giant cells in both the foregoing cases possessed the following physical characteristics:

1. The extinction angle varied from 10 to 15 degrees.

2. Some crystals were in the orthorhombic and some in the monoclinic system.

3. The crystals had a higher refractive index than Canada balsam (1.54). Talc crystals possess an index of refraction of 1.589 along two axes.

4. The crystals were anisotropic.

5. The crystals were roughly of the same magnitude and morphologic appearance as those in talcum powder.

Further evidence of a mineralogical nature was obtained by incineration. Paraffin sections, unstained, were incinerated at about 400 C.

for five hours on two successive days. Examination revealed no alteration in the crystals.

The significant results obtained in the study of these two cases led to an investigation of all the records of foreign body reactions in the files of this laboratory. During a period of nine years only three other cases had occurred in which crystals resembling those in talcum powder were apparently responsible for clinically important lesions. Several other cases were discovered in which a reaction to crystals was present, but it was overshadowed by that due to suture material.

Case 3.—A 50 year old woman had had a blue spot on the mucocutaneous border of the lower lip for a number of years. There had been a slight increase in the size of the lesion during a few months previous to an operation on the lip at another hospital four weeks prior to examination in the present instance. The pathologic diagnosis was basal cell carcinoma.

Examination showed on the left of the median line of the lower lip, a healed surgical scar 1 cm. in length. One portion of the scar, 0.4 cm. in diameter, was firm and nodular. In the left side of the neck there were from two to five enlarged palpable lymph nodes. The submaxillary gland on the left side was slightly larger than that on the right. The clinical diagnosis was recurrent carcinoma.

A V-shaped excision of the lesion was made, with later dissection of the submaxillary triangle.

Microscopic Examination.—A segment of the lip containing a small indurated area of mucosa was sectioned, and the sections were treated with the hematoxylin-eosin stain. Dense scar tissue extended into the muscle from the corium, with fairly numerous foreign body giant cells present. Laterally, whorl-like arrangements of fibroblasts surrounded the foreign body giant cells. The pseudotubercle formation was not well advanced. Numerous anisotropic crystals were surrounded by and contained within the foreign body giant cells.

The diagnosis was a foreign body reaction. The diagnosis of the lesion in tissue obtained in the submaxillary dissection was hyperplasia of the lymph nodes and slight chronic inflammation of the submaxillary gland. (No anisotropic crystals occurred within the lymph nodes.)

Case 4.—A 54 year old man had had, fifteen years previously, a furuncle on the left side of the lower lip about 2 cm. from the mucocutaneous line. Two years prior to examination in the present instance, a small nonulcerated crater formed in the center of the old cicatricial tissue. This was treated with radium at that time. About one month before examination, an excision of scar tissue was made at another hospital. The pathologic diagnosis was carcinoma.

An excision of recurrent carcinoma and plastic repair were made. The specimen consisted of a small triangular piece of lip covered by skin and mucous membrane. The skin showed a small depressed area with some thickening and induration beneath it.

Microscopic Examination.—Sections were prepared with the hematoxylin-eosin stain. Dense scar tissue extended from the corium to the muscle. Within the scar tissue were small groups of foreign body giant cells surrounding and containing anisotropic crystals. Scattered lymphocytes were present.

In one section a small focus of tumor was surrounded by dense fibrous tissue in which numerous anisotropic crystals were present within foreign body

giant cells. The tumor tissue was arranged in the form of hair follicles, occupying about three quarters of a low power field. Invasion was fairly active. The cells were small, with oval nuclei containing fine chromatin granules. The cytoplasm was scanty; the cell outlines, indistinct. Mitotic figures were not numerous. There was palisading of cells at the edges.

The diagnosis was chronic inflammation, scar tissue, a foreign body reaction and a small focus of basal cell carcinoma, apparently of the hair matrix type. (This focus was found only after many sections had been examined.)

CASE 5.—A 23 year old man had a swelling on the right side of the perineum, which appeared three weeks prior to his first admission to the hospital. This steadily increased in size and became tender. Examination disclosed that in the right anterior perineal region there was an egg-sized indurated tender swelling with fluctuation at the center. There was no induration along the wall of the rectum. Incision and drainage were carried out.

The patient was again admitted two weeks later. An opening was made in the fistula seen at the site of the previous incision for drainage in the right anterior perineal region. A probe was passed along the left wall of the rectum, but no internal opening could be demonstrated. The condition was diagnosed as blind external fistula in ano.

Radical excision was performed.

The specimen consisted of a piece of skin and subcutaneous fat, 4 by 2.5 by 1.5 cm. The skin, 2.5 by 1 cm., was traversed by an incision which led into a sinus 1.2 by 0.2 cm. in diameter, running the length of the specimen. There was blue discoloration about the incision. The surrounding tissue was fibrotic.

Microscopic Examination.—Sections were prepared with the hematoxylin-eosin stain. The sinus tract was lined by granulation tissue, which was infiltrated with numerous lymphocytes. About the sinus tract was dense scar tissue, also heavily infiltrated with lymphocytes. This fibrosis extended into the fat. Within the fibrous tissue were numerous anisotropic crystals, many of which were within numerous foreign body giant cells. Crystals and giant cells were close to the sinus.

The diagnosis was a fistula with chronic inflammation and a foreign body giant cell reaction.

All of the crystals in the last three cases resembled those found in the first two. Furthermore, in morphologic character they were strikingly similar to talc crystals which were mounted in glycerin and examined under the microscope.

EXPERIMENTAL STUDY

Three adult mice were used. In each mouse 1 cc. of a sterilized 10 per cent suspension of talcum powder in distilled water was injected subcutaneously into the abdominal wall, as well as intraperitoneally. At the end of seven weeks the mice were chloroformed and examined. The findings were more or less similar in all. Firm opaque white nodules about 0.3 cm. in diameter were found in the subcutaneous tissues of the anterior abdominal wall at the point of injection. Within the peritoneal cavity, similar nodules, covered by smooth serosa, were found on the serosal surfaces of the spleen, liver and small and large intestines, as well as within the mesentery of the small intestine and omentum. These nodules measured from 0.1 to 0.3 cm. in diameter. Some of the larger nodules, both

in the anterior abdominal wall and within the peritoneal cavity, possessed centers of unaltered dry powder.

Microscopic Examination.—Sections were prepared with the hematoxylin-eosin stain. The nodules described in the macroscopic examination were composed of granulomatous tissue, with numerous foreign body giant cells surrounding and containing anisotropic crystals similar to those found in the surgical specimens described. There was much fibroblastic proliferation about the crystals. At times a rather thick fibrous capsule formed at the periphery. In addition, scattered endothelial cells, lymphocytes and a few polymorphonuclear leukocytes were visible. There was invasion of the fat of the mesentery of the small intestine and of the omentum by the granulomatous tissue.

There was localized compression of the spleen and liver by large nodules but no invasion of parenchyma. In some of the larger nodules, crystals were present centrally, with a few necrotic phagocytic cells visible. Fibroblasts and foreign body giant cells were present at the periphery. No tubercle formation was seen, but this was probably due to the fact that the time during which the crystals remained in the animals had been comparatively short.

COMMENT

In the first two cases, the results obtained following incineration showed that the crystals were mineral. This, together with their physical characteristics, makes it practically certain that talc crystals were present. In the last three cases, the crystals were found to be morphologically identical with those in the first two cases and with talc crystals examined under the microscope. That talc crystals may produce lesions similar to those found in the cases studied is brought out by the results obtained in animal experimentation.

It is of great interest that in the first two cases the length of time necessary to produce clinically perceptible masses ranged from five to seven years. This long period of time might be the cause of clinical error in that the possibility of the introduction of a foreign body like talc during the previous operation might be forgotten.

An analysis of the cases affords much instruction. One is struck by the varied character of the cases in which talc crystals introduced a cause of diagnostic error. In the first case, an exploratory laparotomy was done for a suspected tumor of the abdomen. Even examination during the operation did not reveal the error, which was further masked by the diagnosis of tuberculosis suggested by the frozen section. It was only after the section was examined under crossed Nicol prisms that the true nature of the lesion was suspected.

In the second case, the patient had suffered from hyperthyroidism, and it was natural that the nodules palpable in the neck were thought to be dangerous, although no symptoms of hyperthyroidism were present. Here, too, the presence of a foreign body was unsuspected.

In the next two cases lesions were presented in still another region, the lip. In the first of these, recurrent carcinoma was suspected, but the

nodule was found to be caused by a foreign body reaction to crystals. On the other hand, the presence of crystals in the second case caused a lesion to be suspected which alone would probably have been missed for some time and in this way proved to be a boon to the patient.

While the last case, one of a fistula in ano, presented no difficulty in diagnosis, it offered evidence that talc crystals in some instances may be responsible for keeping sinuses open.

Although cases of the type described are admittedly rare (5 in 30,000) the surgical lesions suggest that the indiscriminate use of talcum powder on gloves is to be avoided. Washing the gloves before entering the operative field tends to prevent such granulomas. In view of the extensive use of the dry technic, the rarity of such a complication suggests the possibility of individual variation in the reactions of patients.

The cases offer another example of the harmfulness of silicates in the human body. While rare, the lesions may be a cause of diagnostic error.

SUMMARY

Two cases have been presented of granuloma caused by anisotropic crystals shown to be talc (magnesium silicate—$3\,MgO.4SiO_2.H_2O$). Three cases have been described of similar lesions in which the crystals were morphologically similar to talc crystals. Lesions similar to those found in the foregoing cases were produced by talc in mice.

An analysis of the cases revealed the diagnostic errors caused by talc crystal granuloma under varied circumstances.

The value of examination of suspicious sections under crossed Nicol prisms is stressed.

The indiscriminate use of talcum powder in the operating room may produce granulomatous lesions.

PATHOLOGIC CHANGES IN THE TISSUES OF THE DOG FOLLOWING INJECTIONS OF RATTLESNAKE VENOM

HAROLD N. TAUBE, M.D.
AND
HIRAM E. ESSEX, PH.D.
ROCHESTER, MINN.

The pathologic changes produced in the tissues by rattlesnake venom have not been studied minutely. Mitchell and Reichert [1] in 1886, Flexner and Noguchi,[2] in 1902, and others have investigated rattlesnake venom, but they were concerned chiefly with its physical and chemical properties and its physiologic and toxicologic effects. With few exceptions, they made only macroscopic observations, omitting histologic studies.

This paper presents the results of a study of the microscopic changes in the tissues of dogs after injections of rattlesnake venom (crotalin). The purpose was to determine the pathologic effects of the venom and the types of tissue affected, and, if possible, to show a relationship between these and the physiologic disturbances and postmortem observations seen by Essex and Markowitz [3] following such injections.

Phisalix [4] stated that Nowak [5] was the first to make histologic studies of this kind. The venom used by him was a mixture obtained from a number of snakes and scorpions, which was heated to 80 C. Obviously such a method shows the combined effects of several venoms rather than the specific action of any one of them. Moreover, heating to 80 C. reduces the toxicity of the venom, as shown by Flexner and Noguchi.[6] Pearce [7] demonstrated that rattlesnake venom (Crotalus

From the Division of Experimental Medicine, Mayo Foundation.

1. Mitchell, S. W., and Reichert, E. T.: Researches upon the Venoms of Poisonous Serpents, Smithsonian Contributions to Knowledge, Washington City, 1886, vol. 26, no. 647.

2. Flexner, S., and Noguchi, H.: Univ. Pennsylvania M. Bull. **15**:354, 1902-1903.

3. Essex, H. E., and Markowitz, J.: Am. J. Physiol. **92**:317, 329, 698 and 705, 1930.

4. Phisalix, Marie: Animaux venimeux et venins, Paris, Masson & Cie, 1922, vol. 2, p. 602.

5. Nowak, J.: Ann. Inst. Pasteur **12**:369, 1898.

6. Flexner, S., and Noguchi, H.: J. Path. & Bact. **10**:111, 1905.

7. Pearce, R. M.: J. Exper. Med. **11**:532, 1909.

adamanteus) injected intravenously into rabbits in properly graded doses over a period of from one to six days produced changes in the glomerular capillaries. These changes were hemorrhagic and exudative in character, features either of which might predominate. There were intraglomerular and capsular hemorrhages, sometimes with the presence of fibrin. The exudative lesion occurred with or without hemorrhages, and occasionally the exudate was within and limited to the capillary tuft and all the elements of the blood appeared in it.

METHOD

Gross and microscopic observations were made of the tissues of several dogs which had been given injections of various doses of venom for the primary purpose of studying the physiologic reactions (Essex and Markowitz). Additional material was secured by injecting into three dogs intravenously lethal doses of venom. These dogs died in eight minutes, ten hours and twenty hours, respectively. For control material a normal dog was killed under ether anesthesia. Specimens of all the parenchymatous tissues were taken immediately after death. These were fixed in solution of formaldehyde U. S. P. (1:10), embedded in paraffin and sectioned and stained with hematoyxlin and eosin. Following crotalin poisoning of two of the dogs examinations were made of the brain and upper part of the spinal cord. Sections were taken at various levels and treated as described; two sets of sections were made at each level, one set being stained with eosin and the other with hematoxylin.

SYMPTOMS; OBSERVATIONS AT NECROPSY

The intravenous injection of crotalin was regularly followed by marked evidence of weakness, illness and torpidity. There were repeated vomiting, defecation and urination of fluid, mucus and large quantities of blood. Circulatory deficiency was evidenced by a progressive fall in blood pressure, ending in death.

The typical changes observed post mortem were as follows: Marked rigor mortis was present. Numerous petechial hemorrhages were seen on the inner surfaces of the upper and lower eyelids. The tongue showed similar hemorrhages. All the organs in the thorax revealed varying degrees of petechial and diffuse hemorrhages. When death occurred within a few minutes after injection of the venom such hemorrhages were less severe. Hemorrhages were usually present beneath the epicardium of both the auricles and the ventricles, the endocardium usually being similarly affected. Hemorrhages could be seen over the diaphragm, especially over the central tendon.

In the peritoneal cavity practically all the organs contained superficial hemorrhages. The serous surface of the entire alimentary tract was usually dotted with hemorrhagic areas, but the descending colon usually presented the most severe hemorrhages. In the interior of the stomach, small intestine and colon large areas of hemorrhage were present, and large amounts of blood were usually found in the small intestine. Multiple diffuse and punctate hemorrhages were seen in the brain. The blood was not clotted in the heart and large veins. The pancreas revealed severe hemorrhagic infiltration. The liver was usually mottled and purplish and on section appeared to be extremely congested. The gallbladder sometimes showed extensive hemorrhages under its serous surface. The spleen

was usually extremely contracted and slate-gray. The external color of the kidneys was usually gray, but subcapsular hemorrhages were sometimes present. On section reddish streaks were usually seen in the medulla, and the renal pelvis occasionally contained submucous hemorrhages. The urinary bladder was invariably extremely contracted. The adrenal glands usually appeared normal, but on section punctate hemorrhages were sometimes found, especially in the medulla.

HISTOLOGIC OBSERVATIONS

In view of the marked hemorrhagic nature of the changes found at necropsy the presence of the same features was to be expected in the microscopic sections.

Gastro-Intestinal Mucosa.—Following immediate death from crotalin poisoning there was a marked increase in vascularity, particularly in the submucous and muscular layers. The minute vessels were congested and had intact walls lined by swollen epithelium. The muscular layer appeared edematous. In poisoning of longer duration the cells in the mucosa showed granular degeneration; in some cells the nuclei had disappeared, and the cells were necrotic. Moderate leukocytic infiltration was observed. Numerous congested vessels were present throughout the tissue. Some of the capillaries gave evidence of definite breaks in the endothelial walls.

The changes described were found in the stomach, small intestine and colon. Hemorrhages were particularly numerous in and beneath the mucosa of the colon. In this region necrosis and disintegration of epithelial cells had produced areas of ulceration extending into the submucosa (fig. 1 *A*).

Pancreas.—There was engorgement of the blood vessels throughout the tissue of the pancreas. The capillaries of the acini and the islands of Langerhans were distended and engorged. There was moderate perivascular edema. In poisoning of longer duration areas of hemorrhage were seen between the individual acini. There was visible disintegration in the walls of the capillaries, venules and arterioles. Many of the acini appeared disintegrated and showed both granular degeneration and necrosis.

Great Omentum.—Following rapid poisoning the vascularity was greatly increased. There was engorgement of all vessels, with an increase in the number of open capillaries. In poisoning of longer duration congestion had progressed to hemorrhage, and extensive infiltration of blood was seen throughout the tissue. Many of the congested vessels had visible breaks in their walls.

Spleen.—Little change was seen in the splenic tissue following rapid poisoning. In poisoning of longer duration there were hemorrhages into the splenic pulp, the vascular channels were congested, and there was evidence of extensive necrosis. The capsule was edematous.

Kidney.—In rapid poisoning there was marked congestion of all the capillaries. In some of the glomeruli this was so marked that they appeared as masses of erythrocytes and the glomerular structure was obscured. The cells lining Bowman's capsule had swollen nuclei, and the endothelium of many of the blood vessels was swollen. The cells of the tubules in both the cortex and the medulla showed parenchymatous degeneration.

In poisoning of longer duration there were marked granular degeneration and necrosis of the tubules, particularly in the subcapsular zone. The proximal convoluted tubules were affected most. Some of these contained débris; in others the entire lining was separated from the basement membrane and constituted a granular mass of cellular débris. The same congestive features were present as in

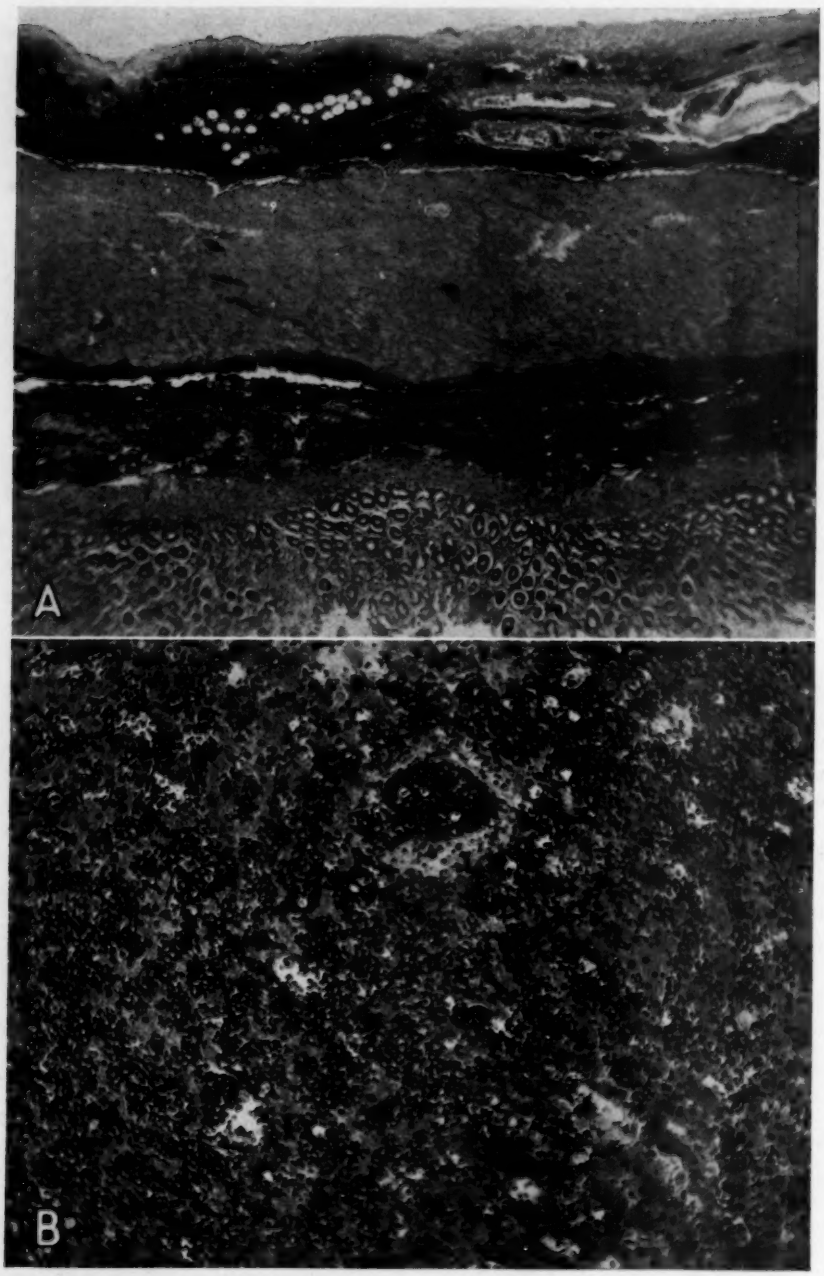


Fig. 1.—*A*, colon showing severe hemorrhage into the submucosa and subserosa (× 25). *B*, liver showing extensive diffuse intralobular hemorrhage causing distortion of the histologic pattern (× 150).

cases of poisoning of short duration. There were areas of hemorrhage in both the medulla and the cortex. Many of the collecting tubules contained blood, fibrin and serum.

Adrenal Glands.—The capsule was somewhat edematous. There was increased vascularity of the cortex, and the capillaries were greatly distended. Scattered minute extravasations of blood were present in both the cortex and the medulla.

In poisoning of longer duration there was evidence of cellular necrosis in the cortical zone, and extravasations were more numerous. The medulla showed the same congestive and hemorrhagic features as the cortex.

Liver.—The sinusoids throughout the liver were widely distended with blood, and blood was present in both the central and the peripheral zones of the lobules. Hemorrhage was most marked in the intermediate central zones, less so in the periportal zones. The cells of the liver were swollen and gave evidence of granular degeneration. Similar changes were seen in the cells of the biliary ducts (fig. 1 *B*).

In poisoning of longer duration the degeneration had progressed to necrosis. Some leukocytic infiltration was present. The Kupffer cells were swollen and stood out prominently. Some had pyknotic nuclei. The bile ducts contained débris and desquamated cells.

Gallbladder.—The mucosal and muscular layers contained congested capillaries lined by swollen endothelium. Ulcerated areas were present in the mucosa. In poisoning of longer duration necrosis and ulceration of the mucosa were more marked. Hemorrhages were present in the serous surface and to a lesser extent between the muscle fibers.

Bladder.—The lumen contained erythrocytes and desquamated epithelium. The mucosa contained numerous congested capillaries, and extravasations were seen throughout the vesical tissue. There was congestion of the vessels in the muscular layers.

Heart.—The venous channels were engorged, and the number of capillaries visible between the muscle fibers was increased. In cases in which death was delayed, there were extensive areas of hemorrhage from minute vessels, and the myocardium showed marked degeneration and extensive necrosis. Both the epicardial and the endocardial surfaces contained hemorrhages and edema (fig. 2 *A*).

Aorta.—Congestion of the vasa vasorum was seen following rapid death. Following delayed death the adventitia was edematous as well as congested and hemorrhagic. The endothelium lining both large and small arteries was swollen. The endothelial nuclei were rounded and somewhat vesicular in appearance.

Thyroid Gland.—The same hemorrhagic and degenerative changes were seen in this gland as in the other glandular tissues.

Muscle.—With the exception of moderate capillary congestion, no significant changes were seen in skeletal muscle.

Lungs.—Marked diffuse congestion was the chief feature when crotalin poisoning was followed immediately by death. Following delayed death there were congestion, hemorrhages and edema, which affected both the mucosa and the alveolar walls. There was desquamation of bronchial epithelium, and the bronchial lumens contained débris, blood, serum and fibrin. The alveolar spaces contained varying quantities of fluid, deposits of fibrin, and blood. Some evidence of actual necrosis and disintegration of alveolar walls was seen. Moderate infiltrations of leukocytes were present in cases in which poisoning was of longer duration (fig. 2 *B*).

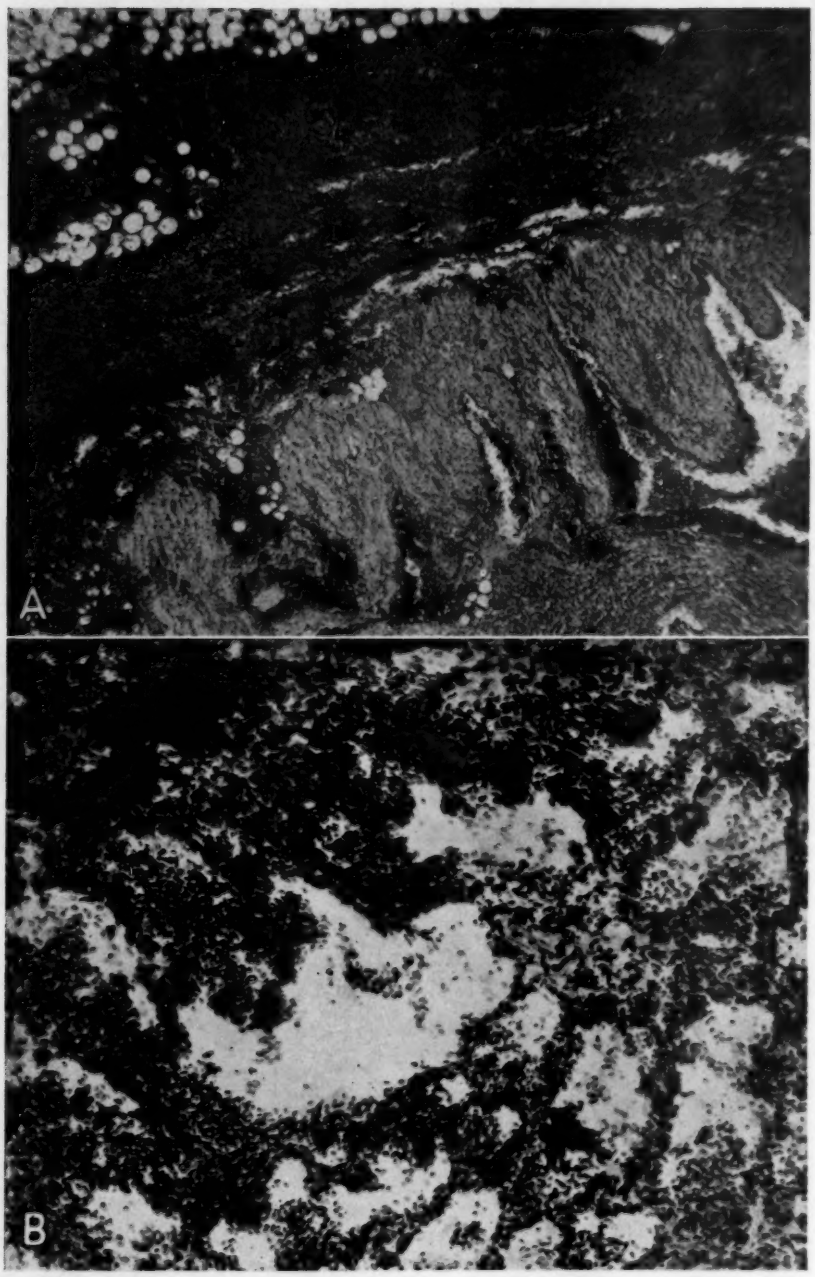


Fig. 2.—*A*, heart showing a large area of hemorrhage in loose tissue over the auricle (× 45). *B*, lung showing marked congestion of interalveolar spaces, with considerable extravasation of blood into the alveoli (× 200).

Brain and Spinal Cord.—Congestion of capillaries and venules was present in both the substance and in the meninges. Hemorrhages were more marked in poisoning of longer duration than following rapid death. Also, in cases in which death was delayed, there was marked evidence of degenerative changes and of necrosis of the ganglion cells in the various areas examined. Chromatolysis was seen in the nuclei, and loss of granulation of the cytoplasm, and in many cells the nuclei were not visible. Both small hemorrhages and extensive diffuse extravasations were present in the meninges.

Summary.—The histologic changes following fatal doses of crotalin were: marked capillary and venous engorgement in all organs, extensive hemorrhages, acute edema of tissues, and granular degeneration and necrosis of parenchymatous tissues, including the central nervous system.

COMMENT

Brainard [8] stated that the blood is uniformly found dissolved after death from rattlesnake bite and is incapable of coagulating to the same extent as in health. Mitchell [9] observed that the blood of animals that live an hour or two after crotalin poisoning becomes incoagulable. In the present experiments the blood did not clot. When death occurred eight minutes after the injection of venom, the blood in the vessels remained fluid, and a sample taken at necropsy had not clotted three hours later. A similar decreased coagulability was observed when death occurred at longer intervals following the injection of venom.

Circulatory manifestations are the outstanding characteristics of poisoning by crotalin. Mitchell [9] made experiments which led to the conclusion that hemorrhage results from the direct effect of the venom on the vascular walls. Mitchell and Reichert found that hemorrhage occurred chiefly from the capillaries, but they were unable to demonstrate actual breaks in the walls. Flexner and Noguchi recognized in crotalin venom an endotheliolytic property, which they called hemorrhagin. This they thought caused hemorrhage by virtue of its lytic action on the endothelium of the capillaries and venules: "The extravasations take place, not by diapedesis, but through actual rents in the walls. That these rents are not simple ruptures seems to be proved by the disappearance as if by solution of the parts of the wall at the point of escape of the corpuscles." Pearce confirmed this by reporting similar observations on the glomerular capillaries.

We have found evidence of the dissolution of the walls of capillaries and venules in various organs and tissue. Microscopically there was evidence of damage to the walls of the capillaries and vessels in each of the tissues studied. There were numerous hemorrhages, and there was visible disintegration of the endothelium. In many instances,

8. Brainard, D.: On the Nature and Care of the Bite of Serpents and Wounds of Poisoned Arrows, Rep. Smithsonian Inst., 1854, pp. 123-136.

9. Mitchell, S. W.: New York M. J. **6**:289, 1867-1868.

edematous fluid resembling serum was seen outside the vascular walls, distending the tissue spaces. Marked granular degeneration was present, and in some instances, necrosis of the cells of the parenchymatous tissues. It was noted that extensive hemorrhages, degeneration and necrosis were more marked in cases in which death was somewhat delayed. When death occurred promptly following injections of venom, marked congestion of the capillaries and vessels throughout all the organs was the predominant feature. Hemorrhage and degeneration were less marked probably because death occurred promptly.

Both the gross and the microscopic evidence indicate that crotalin exerts a powerful toxic effect on the parenchymatous cells and particularly on vascular endothelium. This effect accounts for the marked circulatory disturbances which precede death, as well as for the engorgement, edema and hemorrhages that characterize the pathologic picture in the tissues. It is significant that when death was not immediate (Essex and Markowitz) the dogs showed signs of marked circulatory disturbances ante mortem: a rapid feeble pulse, falling blood pressure, and marked concentration and decreased coagulability of the blood. Both the vomitus and the liquid defecations contained blood. Weakness, prostration and other evidence of shock were present. These effects so closely resembled those produced by histamine that one major purpose of the investigation was to determine whether histamine or some other substance in the venom was responsible for its effects on the circulation. It is likewise significant that both the gross and the microscopic changes in tissues were of the same nature as Moon [10] and his colleagues found following shock produced by various methods. Atchley [11] reported an instance of rattlesnake bite in which the venom apparently directly entered a vein. The patient had all the clinical evidence of shock, and his condition was so interpreted by the author.

Kellaway [12] recently showed that the venom of various Australian snakes acts principally as a circulatory depressant. The fall in blood pressure and other features resembled so closely the effects of the action of histamine that the author took pains to determine that histamine was not the substance causing them. He demonstrated that the action was not on the heart or on the vasomotor system but was peripheral. The coagulability of the blood was reduced. Marked swelling and edema of the part bitten, pulmonary congestion and

10. Moon, V. H.: Ann. Int. Med. **8**:1633, 1935; Arch. Path. **14**:360, 1932; **21**:565, 1936.

11. Atchley, D. W.: J. A. M. A. **95**:385, 1930.

12. Kellaway, C. H.: M. J. Australia **1**:678, 1934; **2**:74 and 249, 1934; Australian J. Exper. Biol. & M. Sc. **12**:47 and 177, 1934; **13**:17 and 205, 1935; **14**:57, 1936.

edema, bloody fluid in serous cavities and visceral congestion and hemorrhages were the characteristic morphologic changes seen at necropsy.

In view of these considerations it appears that other venoms as well as crotalin act directly on vascular endothelium and tissue cells. They cause the capillaries and vessels to dilate and to become abnormally permeable to the fluids of the blood. Landis [13] found that agents which injure capillary endothelium cause increased permeability of the walls. In many instances the injury produced by venom is so severe as to cause dissolution of the endothelium, resulting in extravasations. These effects produce marked engorgement of the minute vessels, edema and hemorrhages. The result is a disparity between the volume of blood and the volume capacity of the vascular system, a disparity which, as was recently emphasized by Moon, manifests itself in the syndrome of shock.

The observations that were made in this study on the pathologic changes resulting from experimental poisoning with crotalin attach directly to the accumulated body of evidence regarding the agents and conditions which cause endothelial injury, their physiologic effects and the resulting pathologic changes.

SUMMARY

In cases in which death rapidly follows poisoning by crotalin the various tissues give evidence of engorgement of all their blood vessels, the walls of which are intact and lined by swollen endothelial cells. Granular degeneration is present, affecting parenchymatous organs and mucosa. The blood in the vessels is not clotted, nor does it clot within three hours.

In cases in which poisoning is of longer duration there is visible disintegration of vascular walls. Hemorrhage is a prominent feature in all tissues of the body. Degeneration and necrosis of parenchymatous tissues are prominent. Leukocytic infiltration, with many monocytes, is associated with the degeneration and necrosis. The blood loses its coagulability and remains fluid. It is probable that the endothelial cells first contract, then swell and finally burst and dissolve, leaving gaps in the wall of the blood vessel.

Crotalin is an active poison which contains a principle that may be regarded as a cytolysin for endothelial cells of blood vessels and for other protoplasmic structures with which it comes in contact. Its effect on the walls of minute vessels results in the physiologic manifestations and changes in tissue which are characteristic of certain types of shock.

13. Landis, E. M.: Am. J. Physiol. **81**:124, 1927; **82**:217, 1927; **83**:528, 1928.

Case Reports

ACUTE HEMORRHAGIC ENCEPHALITIS ASSOCIATED WITH A MEDULLOBLASTOMA

CHARLES CRAMER, M.D., BROOKLYN

Acute hemorrhagic encephalitis is a condition which, while not rare, is sufficiently infrequent to warrant recording. Of increasing interest in the case to be reported is the presence of a tumor of the brain, disclosed at autopsy, an association that is extremely rare as far as my knowledge of this disease is concerned.

REPORT OF CASE

A 23 year old white man, a bookkeeper, was admitted to St. John's Hospital, complaining of fever and of pain in the left side of the chest of a day's duration.

Five months prior to this, he was admitted to the New York Neurological Institute, where the following history was obtained: One year previous to admission it was noticed that the patient would go to sleep in the daytime at his work. This somnolence increased. During the six weeks before admission his memory became progressively poor and his speech thick. He did not mispronounce words but talked more slowly. For several months he had diplopia in the morning, seeing objects side to side. He frequently wept over trivial incidents. One month before admission he had a cataplectic-like attack, associated with an emotional upset, the nature of which he did not remember. His weight increased from 185 to 245 pounds (from 84 to 111 Kg.) in the year prior to admission.

Examination at the institute showed an obese patient with masklike facies. There was diminution of associated movements in the upper extremities. The speech was slow and monotonous. The pupils were unequal and irregular and reacted very poorly in accommodation. There was a fine rhythmic tremor of the lips and tongue. There was definite mental retardation.

The urine was normal. The leukocyte count was 12,700, with polymorphonuclears 60 per cent. The Wassermann reaction was negative. The basal metabolic rate was —8, taken on one occasion only. Roentgen examination of the skull did not reveal evidence of an intracranial lesion.

Twelve days after admission he contracted lobar pneumonia, from which he made an uneventful recovery. About three weeks later he was discharged with a diagnosis of chronic epidemic encephalitis, with disturbances in behavior and idiopathic narcolepsy and cataplexy.

During the five month period between his discharge from the New York Neurological Institute and his admission to this hospital, he was mentally dull. His present illness began five days before admission, when he fainted. During the next five days he did not feel well and remained in bed most of the time, suffering from anorexia and general malaise. A slight cough developed, which cleared up two days before he entered the hospital. Twenty-four hours before admission he became feverish and had pain in the left side of the chest.

From the Pathological Laboratories of St. John's Hospital.

The face was flushed, and the lips were cyanotic. Many large crusted papules covered the face. The eyes, ears and nose were normal. There was no rigidity of the neck. There was diminished resonance over both sides of the chest, but no areas of dulness were detected. The breath sounds were suppressed over both sides, and dry crackling râles were heard on both sides anteriorly and posteriorly. The heart was normal. The temperature was 105 F., the pulse rate 150, the respirations 48, and the blood pressure 110 systolic and 70 diastolic.

The urine showed albumin (4 plus), sugar (4 plus), and granular and cellular casts in large numbers. The hemoglobin was 85 per cent. The white cell count was 11,600, with polymorphonuclears 80 per cent. A culture of the blood was negative.

The clinical impression was lobar pneumonia, bilateral. The patient became progressively and rapidly worse. He lapsed into coma shortly after admission. The temperature remained between 105 and 106.6 F. He continued to be cyanotic, and the respirations became labored. He was placed in an oxygen tent twenty-four hours before death. Death occurred about forty hours after his admission to the hospital.

Autopsy.—The autopsy was performed eight hours post mortem. The body was that of a well developed white man in the third decade of life, weighing about 250 pounds (113.5 Kg.). The calvarium was large but otherwise normal. The skin of the face had a number of excoriations, with crust formation. The superficial lymph nodes were not palpable, and there was no peripheral edema.

On removal of the sternum, about 150 cc. of pale red fluid was found in the left pleural cavity, and a slight increase of similar fluid was found in the right pleural cavity. The pericardium was normal.

The right lung weighed 650 Gm.; the left, 500 Gm. The lower lobes of both lungs and the posterior portion of both upper lobes exhibited a dark reddish discoloration. Numerous small subpleural hemorrhages were scattered over the surface of both lungs. The dark areas were firm, but only an occasional small area of consolidation was felt. On section, the red areas appeared wet, congested and slightly granular. The bronchi showed marked congestion.

The heart, pancreas, spleen, adrenal glands, gallbladder, kidneys, bladder and prostate did not show gross abnormalities.

The liver weighed 2,200 Gm. It was enlarged and firm and had a smooth shiny capsule, which was mottled with pale yellow areas. On section, the organ had a pale red color, giving the impression of fatty infiltration.

Except for a moderate number of subepithelial hemorrhages in the mucosa of the stomach, the gastro-intestinal tract was normal.

When the calvarium was opened, the brain was seen to lie in its natural position. The dura mater and the leptomeninges were normal, and there was no evidence of hemorrhage over the surface of the brain. Coronal sections through the organ revealed a uniform and striking picture. Scattered irregularly through the brain, but without localization to one region, were numerous circumscribed hemorrhages varying from pinpoint size to a diameter of 3 mm. These were limited entirely to the white substance. There were no areas of massive hemorrhage. The large vessels at the base of the brain were normal, and there was no evidence of thrombosis, embolism or sclerosis. In the region of the basal ganglions on the left side there was an area of softening about 1 cm. in diameter. This area was well circumscribed, and no hemorrhages were seen in this region or in the region of the basal ganglions on the right. The pituitary gland was grossly normal.

Anatomic Diagnosis.—The diagnosis was: Multiple capillary hemorrhages of the brain (hemorrhagic encephalitis) and focal encephalomalacia (medullo-

blastoma) involving the left basal ganglions; congestion and edema of the lungs, congestion of the bronchi, bilateral subpleural hemorrhages, and patchy consolidation; chronic interstitial splenitis and acute splenitis; cloudy swelling of the kidneys; fatty degeneration of the liver, and subepithelial hemorrhages of the stomach.

Histologic Examination.—Sections through the lower lobes of the lungs and the lower portions of the upper lobes showed marked hemorrhage into the alveolar spaces, with infiltration by a few large mononuclear cells. There was marked congestion of the blood vessels of the septums. There was no acute inflammatory exudation, although in some areas a few of the alveoli showed a slight infiltration by polymorphonuclear cells. One section showed a large area of hemorrhage, adjacent to which there was a thrombosed blood vessel showing beginning hyalinization of the thrombus.

Sections of the brain showed numerous capillary hemorrhages entirely confined to and widely distributed through the white matter. The hemorrhages, for the great majority, were of the "ball hemorrhage" type. There were no definite "ring hemorrhages," but in a few instances an area of solid hemorrhage was less dense in the center than in the periphery. The hemorrhages were discrete, and there was no tendency for them to become confluent. In a few instances an area of hemorrhage showed the remains of a central blood vessel. The surrounding tissue showed no evidence of reactive inflammation or of perivascular demyelinization. The intact capillaries showed edema of the Virchow-Robin spaces. There was no evidence of lymphocytic exudation in this region.

Sections through the area grossly described as an area of softening in the region of the basal ganglions on the left side showed an anaplastic tumor growth composed of loosely textured alveoli made up of hyperchromatic spindle-shaped and oval-shaped cells, many of which showed a pseudorosette formation, suggesting a medulloblastomatous type of glioma.

Sections of the pituitary gland showed a well preserved pars nervosa and pars intermedia. The capillaries of the anterior lobe were dilated and congested. There was no evidence of adenomatous or malignant change in the anterior lobe. An occasional small area of cystic degeneration was seen, but the possibility of artefact cannot be ruled out.

Sections of the liver showed marked infiltration of fat throughout, more marked around the central veins.

The heart, spleen, kidneys and bone marrow did not show any marked histologic change.

The outstanding observations were: acute hemorrhagic encephalitis and medulloblastoma of the brain; congestion and intra-alveolar hemorrhage of the lungs and a recent small area of infarction in one lung; congestion and edema of the spleen; fatty infiltration of the liver, and cloudy swelling of the kidneys.

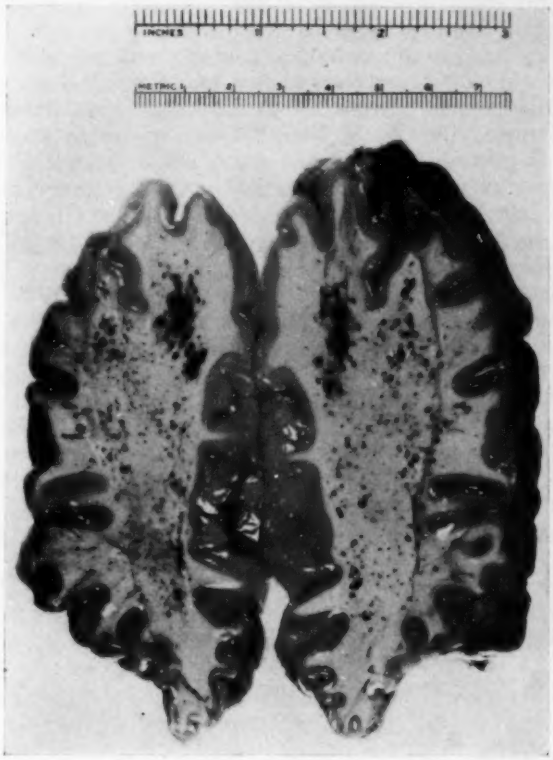
COMMENT

The pathologic picture of multiple capillary hemorrhages of the brain has been reported following such diverse conditions as: measles, scarlet fever, typhus, dysentery (Parnell and Dudley[1]; Musser and Hauser[2]); trauma to the head with or without skull fracture (Bennett

1. Parnell, R. J., and Dudley, S. F.: Lancet **1**:190, 1920.
2. Musser, J. H., and Hauser, G. H.: J. A. M. A. **90**:1267, 1928.

and Hunt;[3] Osnato and Giliberti[4]); fat embolism after fractures; poisoning with arsenic, alcohol, phosphorus and methyl chloride (Scott and Moore;[5] Glaser, Imerman and Imerman;[6] Bender and Schilder[7]); hemorrhagic or venous infarction of the brain (Baker[8]), and purpura haemorrhagica (Alpers and Duane[9]).

Recently Baker[8] reported a series of twenty cases in which the aforementioned causes were carefully eliminated and to which he applied the term "true hemorrhagic encephalitis." The etiologic factors in these cases were not definitely determined, although a virus was.



A section through the brain, showing the small discrete hemorrhages and their sharp localization to the white substance.

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3. Bennett, A. E., and Hunt, H. B.: Arch. Surg. **26**:397, 1933.
4. Osnato, M., and Giliberti, V.: Arch. Neurol. & Psychiat. **18**:181, 1927.
5. Scott, E., and Moore, R. A.: Am. J. Syph. **12**:252, 1928.
6. Glaser, M. A.; Imerman, C. P., and Imerman, S. W.: Am. J. M. Sc. **189**: 64, 1935.
7. Bender, L., and Schilder, P.: Arch. Neurol. & Psychiat. **29**:990, 1933.
8. Baker, A. B.: Am. J. Path. **11**:185, 1935.
9. Alpers, B. J., and Duane, W., Jr.: J. Nerv. & Ment. Dis. **78**:260, 1933.

isolated from the brain in one case. The prevailing opinions at the present time, although no conclusive evidence has been offered, are in favor of virus infection, bacterial infection or toxicosis. I believe the case reported here satisfies the criteria as set forth by Baker and am inclined to regard it as one of true hemorrhagic encephalitis. The histologic picture, coupled with the absence of any history of recent acute infection, trauma to the head, fracture or ingestion of poison, seems to substantiate this claim.

One should realize that there is no constant clinical picture. The signs and symptoms make an abrupt appearance in a previously healthy person. In the cases reported by Baker, headache, lassitude and slight elevation of temperature were the chief initial symptoms. The occurrence, in some cases, of nausea, vomiting, malaise, chills, sweating, difficulty in swallowing, diarrhea and abdominal pain adds to the complexity of the clinical picture. The physical signs likewise present marked variation. Pyrexia is nearly always present. Convulsions of some kind are recorded in 60 per cent of Baker's cases. Ocular disturbances, spasticity of the extremities, altered reflexes and signs of meningeal irritation are noted but with less frequency.

The laboratory findings are not pathognomonic. The blood changes are not significant although moderate leukocytosis, varying from 10,000 to 25,000, is usually noted. The cerebrospinal fluid may offer valuable aid, but the findings are by no means decisive. Increased pressure and pleocytosis are present in some cases. The spinal fluid is usually clear, but if it is blood-tinged, this should arouse suspicion of hemorrhagic encephalitis. The Wassermann reaction of the spinal fluid is as a rule negative. Examination of the urine does not reveal any marked changes.

The patient's course is rapidly and progressively downhill. When the illness is very acute, death occurs within twenty-four hours after the onset of the symptoms. Following the initial symptoms of headache, lassitude and slight elevation of temperature, the patient soon lapses into coma, the temperature rises to great heights, and death occurs shortly thereafter. When the illness is less acute, the duration is usually from one to seven days. The same early prodromal symptoms are present, but the lapse into the unconscious state is somewhat slower.

The patients show a wide variation as to age. In the cases reported by Baker, the youngest patient was 7 months of age; the oldest, 55 years. Sixty per cent of the patients were 25 years of age or younger. There was roughly an even distribution of the cases between the sexes.

It is perhaps safe to state that even though the variations are numerous the onset, clinical course and pathologic picture are fairly typical and the disease presents a definite entity. However, since the clinical picture is so variable, it is not advisable to make the diagnosis without a postmortem examination.

Perhaps a few statements should be made at this point concerning the pathlogic differential diagnosis. Of considerable importance is arsenic poisoning, since the literature contains numerous reports of cases of cerebral accidents following the use of arsphenamine. Thrombosis of numerous blood vessels, hemorrhages into the cord and cerebral cortex, infiltrations by polymorphonuclear cells and lymphocytes and petechiae in other organs are not found in true hemorrhagic encephalitis.

The histologic picture alone, however, is not sufficient evidence to make the differentiation, and one must depend on the history and chemical tests in order to diagnose arsphenamine poisoning.

Cases of cerebral hemorrhage have been reported with primary and secondary purpura. It is of interest to ask whether the subpleural hemorrhages found in the case reported here are a manifestation of purpura or not. The absence in this case of the usual findings in purpura, such as petechiae in the skin, scleras, kidneys, heart and other organs, and of extensive hemorrhages and destruction in both the white and gray substances seems to rule it out. In cases of purpura the laboratory findings concerning the blood would be of value.

The question arises as to the possibility of explaining the hemorrhages on the basis of congenitally weak blood vessels. Forbus [10] studied this question thoroughly and showed that in the cases of spontaneous subarachnoid hemorrhage which he studied and in many of those reported in the literature the hemorrhage was located on the surface of the base of the brain and was due to rupture of a superficial vessel in this region. It seems reasonable to state that if hemorrhagic encephalitis is due to congenital weakness of the blood vessels, one should find other evidence of that weakness in the form of larger hemorrhages from the larger superficial vessels.

The coincidental finding of a tumor of the brain in the present case is food for speculation. Did this tumor play any part in the production of the patient's symptoms, in his death or in the episode five months before, which brought the patient to the New York Neurological Institute? It does not seem likely that a growth of this size could produce a fulminating clinical condition such as was present. If the tumor played a part, what is the connection between it and the recent multiple capillary hemorrhages? Tumor of the brain is not as a rule associated with multiple capillary hemorrhages in the white matter, and one can find no report of a case in which such an association has been noted.

The relation, if any, of the attack of encephalitis five months before death to the present attack is of interest. The pathologic process found in the brain at autopsy was certainly a recent one. If the attack five months before produced the same or a similar picture, I found no evidence of it. One might speculate, however, and suggest that perhaps the first predisposed in some unknown way to the second and final episode.

SUMMARY

A case of true hemorrhagic encephalitis in a 23 year old man, with coincidental finding of a tumor in the brain, is presented. The gross and histologic changes are reviewed in detail.

10. Forbus, W. D.: Bull. Johns Hopkins Hosp. **47**:239, 1930.

PRIMARY CARCINOMA OF THE LIVER CELLS WITH PERITONEAL METASTASIS

F. A. Fiske, M.D., and E. E. Aegerter, M.D., Philadelphia

From a brief review of the literature, it may be concluded that primary carcinoma of the liver is not an exceedingly rare tumor. Well over 600 cases have been reported.[1] It was first accurately described in 1876,[2] but not until 1911 was the classification divided into carcinoma of the liver cells and carcinoma of the small biliary ducts.[3]

There is apparently a strong racial incidence, the percentage being highest in oriental peoples. This may be due to the prevalence of parasitic infections of the liver in orientals. A high incidence, namely, 17 per cent of all cases in which death was due to a malignant growth, has been reported in the Philippines.[4] The disease probably occurs most frequently between the ages of 40 and 60 years,[5] but it has been described in every age period from birth to the age of 83 years.

Cirrhosis is frequently enough concomitant to cause one to suspect that the relationship is more than coincidental. It is seen in association with 85 per cent of carcinomas of the liver cells[6] and with 50 per cent of carcinomas of the bile ducts.[7]

The tumor is more frequently found in the right lobe. Extrahepatic metastasis has been found in only about 20 per cent of the cases. The diaphragm is frequently fixed; the upper border of the liver may be raised and the right kidney pushed downward. Jaundice occurs in about 61 per cent of the cases.[1] Ascites, edema, splenic enlargement, loss of weight, pain, progressive weakness and fever are common symptoms.[8] An increased tolerance for dextrose, with symptoms of insulin shock, has been reported. The liver may be smaller than normal owing to cirrhosis.

The duration is usually from a few weeks to eighteen months, with the majority of the patients dying before a year has elapsed. One

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From the Departments of Surgery and Pathology, Temple University School of Medicine.

1. Beers, D. N., and Morton, J. J.: Am. J. Cancer **24**:51, 1935.

2. Kelsch, A., and Kiener, P. L.: Arch. de physiol. norm. et path. **3**:622, 1876.

3. Yamagiwa, K.: Virchows Arch. f. path. Anat. **206**:437, 1911.

4. Smith, L. W.: Arch. Path. **1**:365, 1926.

5. Ewing, J.: Neoplastic Diseases, ed. 3, Philadelphia, W. B. Saunders Company, 1928.

6. Abel, A. L.: Brit. J. Surg. **21**:684, 1934.

7. Martinez, J. A.: Lancet **2**:1293, 1935.

8. Thompson, S. A.: Canad. M. A. J. **32**:675, 1935.

review stresses the short period of time which elapses between the appearance of the first symptoms and death. In that series, the duration was a matter of weeks rather than months.

Because of the inevitable result without surgical intervention, operation should be attempted when it is possible. There have been cases in which a primary carcinoma of the liver has been successfully removed.[9] In cases in which the tumor is well localized, surgical intervention offers an opportunity for prolonging life. One report of sixteen cases of surgical operation for a primary carcinoma of the liver [10] records four postoperative deaths, six recurrences within eight years and six cures for from three to seven years.

REPORT OF CASE [11]

A white man aged 25 years was admitted to the Temple University Hospital April 12, 1936. For six months there had been a gradually progressive enlargement of the abdomen, with occasional pain about the umbilicus, a loss of 12 pounds (5.4 Kg.) and progressive weakness. There had been increasing dyspnea due to pressure from the abdomen. His physician observed an enlargement of the liver in November 1935. He was studied in another hospital, where the results of the Wassermann, van den Bergh and galactose tolerance tests and the complete blood count were found to be within normal limits. A diagnosis of portal cirrhosis with ascites was made.

The patient presented emaciation, dyspnea, excessive perspiration, apathy, pallor and slight icterus of the scleras. The heart and lungs were normal. There was marked abdominal ascites, with slight tenderness over the liver and an irregular indurated nodular mass in the left epigastrium, which seemed to be infiltrated. The size of the liver and spleen could not be accurately determined. The hemoglobin percentage was 73.7; the red blood cell count was 4,720,000; the white blood cell count was 7,700, with 76 per cent neutrophilic polymorphonuclear leukocytes, 12 per cent lymphocytes and 9 per cent monocytes. The urine was normal except for a slight trace of albumin.

An exploratory laparotomy April 14 revealed many pedunculated round nodules in the peritoneum and omentum, varying in color from red to grayish. A portion of the omentum was removed. On microscopic section, it showed epithelial cells with an arrangement not unlike that of the cells of the adrenal cortex (fig. 1). Bloody fluid to the amount of 7,000 cc. was removed. May 4, another 500 cc. of bloody fluid was removed, the incision being allowed to drain ascitic fluid until the death of the patient, May 12, 1936. The clinical course was one of progressive emaciation, weakness, tachycardia and subnormal temperature with terminal pain and pyrexia. During the latter part of his illness the patient was irrational.

At autopsy, 500 cc. of thin brown fluid was found in the peritoneal cavity. The edge of the right lobe of the liver extended down to the umbilicus. The entire peritoneal cavity and its contents were studded with firm white nodules measur-

9. Love, R. J. M.: Brit. J. Surg. **22**:387, 1934. Abel.[6]

10. Yeomans, F. C.: J. A. M. A. **64**:1301, 1915.

11. Dr. W. W. Babcock gave us permission to report this case.

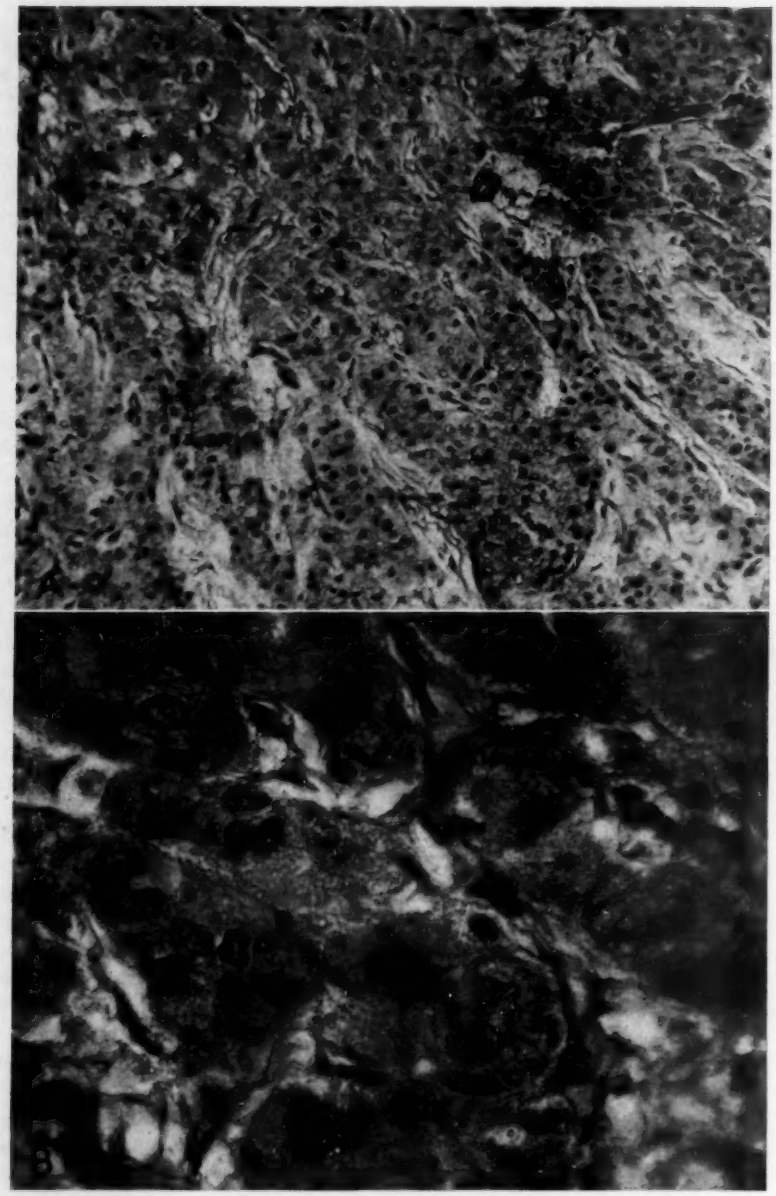


Fig. 1.—Photomicrographs of a metastatic nodule from the peritoneum: *A*, × 100; *B*, ×450. The morphologic character and the arrangement of the cells are suggestive of cells of the adrenal cortex.

ing from 3 mm. to 3 cm. in diameter (fig. 2). In places, these nodules were conglomerate. They were situated in the mesentery, mesocolon, omentum and the peritoneum covering the abdominal viscera and diaphragm. The root of the mesentery, the region about the hilus of the liver and the ligaments attaching the liver to the diaphragm were especially involved. The diaphragm was completely infiltrated with tumor tissue, and there were a few nodules on the thoracic side of the right half of the diaphragmatic dome, under the pleura. The liver weighed 3,250 Gm. The capsule was uninvolved, and the surface was smooth save for an area 13 cm. in diameter on the cephalad surface of the right lobe, where the tumor substance was overlaid with bossing. In the liver substance of the right lobe was a spherical mass. It approached the surface but did not involve the

Fig. 2.—Photograph of the abdominal cavity at autopsy, showing the widespread peritoneal metastasis.

capsule. The mass was firm and pale and incompletely encapsulated. Some areas were discolored green. A complete autopsy was done, and the rest of the organs, including the brain, eyes, lungs, pleura, heart, pericardium, spleen, pancreas, adrenals, kidneys, bladder, testicles, gastro-intestinal tract and bone marrow, showed no evidence of neoplasm.

Microscopic examination of the sections of the tumor in the liver and of the metastatic nodules revealed a disorderly arrangement of liver cells in cords and nests, separated by narrow strands of fine connective tissue fibrils (fig. 3). The cells were of rather uniform size and staining quality. They were polyhedral. Many of the nuclei contained huge nucleoli, which took a brown stain when prepared by the hematoxylin-eosin method. The cytoplasm was finely granular. The sinusoids

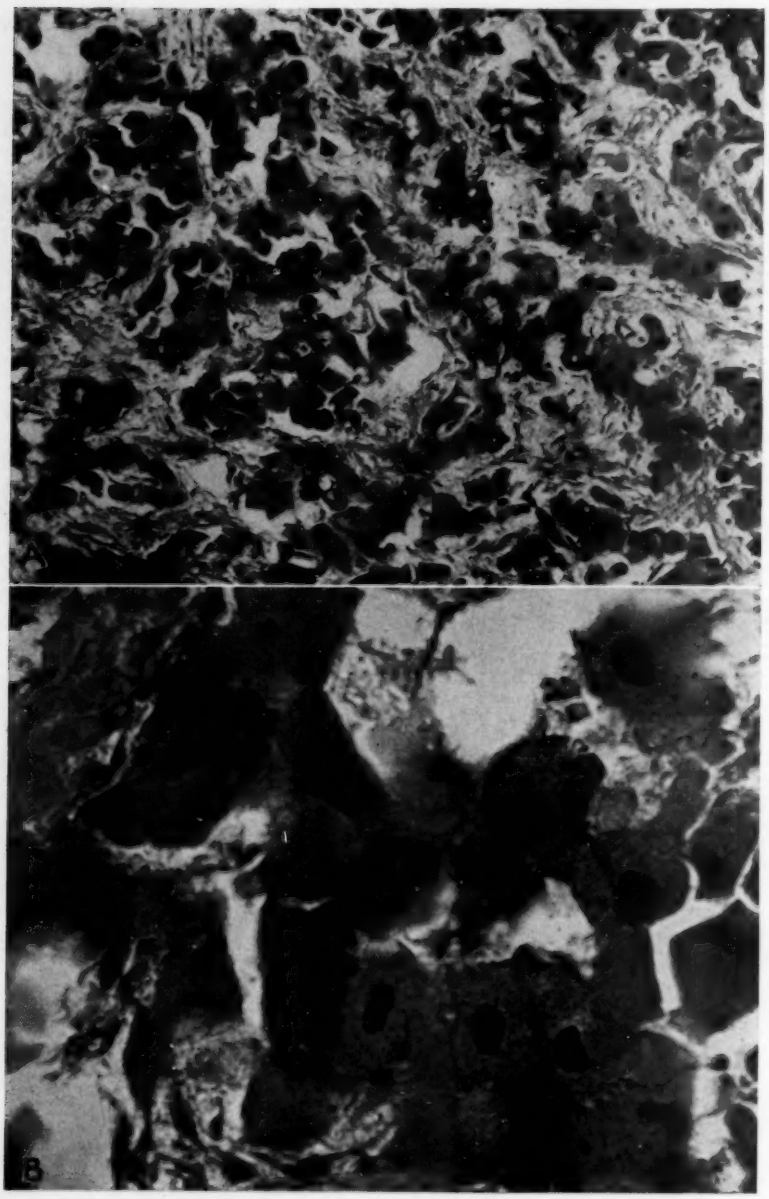


Fig. 3.—Photomicrographs of a section of the primary tumor: *A*, × 100; *B*, × 450. The cirrhosis is evident here.

were lined with endothelial cells. The satellite nodules had well defined fibrous capsules. One nodule was contiguous with, and the cells intermingled with, a small cavernous hemangioma.

This case is reported because of the extensive metastasis in the peritoneum and diaphragm. It seems that the mode of spread was through the lymph vessels. A primary hepatic carcinoma does not usually metastasize outside the liver.[12] Especially is this true of a carcinoma of the liver cells. This may be due, in part at least, to the short duration of the disease. When metastasis occurs it usually occurs in the lymph nodes contiguous to the liver. Other abdominal viscera are more frequently involved than the lungs. One case of metastasis to the brain has been reported.

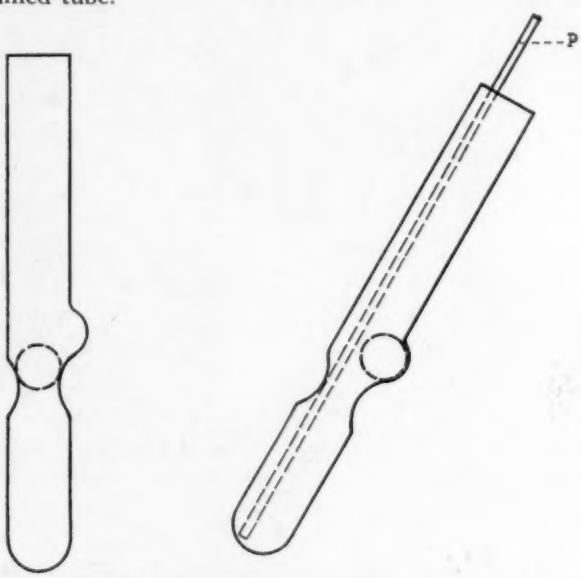
12. Boyce, F. F., and McFetridge, E. M.: Internat. S. Digest. **18**:67, 1934.

Laboratory Methods and Technical Notes

A MODIFICATION OF THE HALL CONSTRICTED TUBE FOR ANAEROBIC CULTURE

WINSTON R. MILLER, LAWRENCE, KAN.

It was found in this laboratory that in using the Hall constricted culture tube [1] for growth of anaerobes it was quite difficult to get an inoculation needle past the marble seal, both in inoculating and in removing portions of the culture. At times it was found necessary to withdraw some of the culture with a pipet. This was impossible with the unmodified tube.



At the left is shown the modified constricted tube of Hall, with the marble seal in place. At the right, the tube is shown inclined, with the marble seal in the off-set, allowing free insertion of the capillary pipet (*P*) into the bottom of the tube.

Hall's constricted tube was modified by blowing a slight off-set in the tube just above the constriction, as indicated in the figure, at the left. This allows free insertion of the inoculation needle or of the capillary pipet.

From the Department of Bacteriology, University of Kansas.

1. Hall, I. C.: J. Infect. Dis. **29**:317, 1921; Univ. California Pub., Path. **2**:147, 1915.

General Review

MECHANISM OF INFLAMMATION

VALY MENKIN, M.D.
BOSTON

The inflammatory reaction consists of dynamic sequences which tend to localize and ultimately to dispose of the causative irritant. I shall restate the significant sequences, with the hope of adding some information on the mechanisms involved, and I shall summarize some earlier observations on the significance of inflammation in the regulation of bacterial invasiveness.

Inflammatory changes are initiated by disturbances in the local exchange of fluids. In an inflamed area the frequently observed initial constriction of the minute blood vessels is soon followed by dilatation. The latter, it has been assumed, is referable to a local axon reflex. Increased passage of plasma into the extracapillary areas occurs as one of the earliest phases of inflammation. Two factors favor the augmented filtration of fluid from the circulating blood. In the first place there is an increase of intracapillary pressure. The measurements of Landis [1] clearly indicated that in the presence of various irritants, such as silver nitrate, heat and cold, there is considerable augmentation in the local intracapillary pressure. For instance, he demonstrated that the pressure on the arterial end of a capillary of a frog may be increased from 14 to 22 cm. of water by application of a crystal of silver nitrate. The studies of Starling [2] and the measurements of Landis demonstrated that capillary filtration is the resultant of two opposed tendencies: the hydrostatic pressure in the capillaries, on one hand, counterbalanced in part, on the other, by the osmotic pressure of the plasma colloids. In view of these facts it is obvious that an increase in pressure within the capillaries would be significant in promoting filtration through the endothelial wall.

From the Department of Pathology, Harvard University Medical School.

An address delivered before the New York Pathological Society, Feb. 25, 1937.

The studies were aided by grants from the Milton Fund, of Harvard University, and from the Wellington Memorial Research Fund and the Permanent Charity Fund, of the Harvard Medical School, and by grants from the Committee for Scientific Research and from the Council of Pharmacy and Chemistry of the American Medical Association.

1. Landis, E. M.: Am. J. Physiol. **93**:353, 1930.
2. Starling, E. H.: J. Physiol. **19**:312, 1895-1896.

Probably an even more striking factor favoring increased seepage into the extracapillary spaces of an inflamed area is an actual change in the endothelial lining which increases its permeability or capacity for passing fluids. Cohnheim [3] called attention to this phenomenon about fifty years ago. The extent of the injury to the capillary wall may be demonstrated in the early phase of the inflammatory reaction by a variety of means. For instance, graphite particles that normally fail to pass through the endothelial membrane readily do so in the early stage of the inflammatory process. Trypan blue and other dyes injected intravenously promptly accumulate in an inflamed area. This accumulation can be demonstrated as early as two minutes after injection of certain irritants.[4] The studies of Hirschfelder [5] and my observations [6] indicate that the enhanced passage of dyes is primarily referable to an increase in endothelial permeability. The increase in plasma filtration from capillaries at a point of injury is open to quantitative measurement. By means of a vital dye it was shown that with some irritants the normal permeability of capillaries is increased about twofold.[6]

An understanding of the mechanism of increased capillary permeability in inflammation is obviously significant and would be of distinct aid in clarifying the concept of the later sequences in the reaction. Several years ago Lewis [7] postulated a type of reaction involving local dilatation and increased permeability of minute vessels by direct action of a single chemical substance, the H substance, liberated from injured tissue. The H substance was presumed to be histamine or at least a substance having similar properties and therefore closely related to it. The conclusions of Lewis and Grant [8] appeared to be based largely on an analogy of the type of reaction obtained by histamine with those obtained by various other injurious agents. When more direct tests were made, in which the effect of the fluid from cutaneous wheals on the contraction of the uterus of the guinea-pig was observed, these investigators stated that they were unable to obtain evidence that histamine was liberated from injured tissue in larger quantities than were found in normal plasma.

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3. Cohnheim, J.: Lectures on General Pathology, London, New Sydenham Society, 1889.

4. Menkin, V.: J. Exper. Med. **53**:647, 1931; **56**:157, 1932.

5. Hirschfelder, A. D.: Am. J. Physiol. **70**:507, 1924.

6. Menkin, V.: J. Exper. Med. **50**:171, 1929. Menkin, V., and Menkin, M. F.: ibid. **51**:285, 1930.

7. Lewis, T.: The Blood Vessels of the Human Skin and Their Responses, London, Shaw & Sons, Ltd., 1927.

8. Lewis, T., and Grant, R. T.: Heart **11**:209, 1924.

Rous and Gilding[9] raised considerable doubt concerning the validity of a hypothesis which refers all local vasodilatation to the action of a single chemical substance liberated within tissues. They reported that the vascular contraction in Bier's spots prevailed over the local reddening induced by mechanical injury, whereas it was without effect on the local vasodilatation induced by cutaneous injection of histamine. More recently, in a preliminary report, Goldschmidt and McGlone[10] studied the failure of reactive hyperemia to occur with arrest of circulation in an atmosphere of oxygen. They compared their findings with the reaction to histamine in a similar oxygenated and ischemic environment. Their observations on the human forearm seem incompatible with the view that the vasodilatation responsible for reactive hyperemia is due to an H substance.

I[11] undertook to determine whether there could be obtained from inflammatory exudates one or more substances which when introduced into normal cutaneous tissue would induce local vasodilatation and increase in the permeability of the endothelial wall as indicated by increase in capillary filtration. Furthermore, I compared the properties of the active fractions which were isolated from inflammatory exudates with histamine in an endeavor to test Lewis' hypothesis. The observations indicated that a diffusible crystalline-like material capable of increasing the permeability of capillaries is present in inflammatory exudates. Exudates were obtained from areas of inflammation induced by various types of irritants, chemical, bacterial or physical (i. e., heat). The cell-free exudate was brought into contact with capillaries of normal skin by cutaneous injection, and a dye indicator, such as trypan blue, was immediately injected intravenously. Prompt and usually homogeneous accumulation of dye in the treated area of the skin was observed.

The active factor in the exudate has been shown not to be the irritant itself. It is carried down with the precipitate resulting from interaction of the exudate with either saturated ammonium sulfate or 20 per cent sodium sulfate, but it is not a protein. It passes through a dialyzing membrane and can be recovered from the concentrated dialysate as an active protein-free crystalline-like material. I have recently been able, by extracting with pyridine and acetone and treating with water or butyl alcohol, to crystallize it, obtaining a substance apparently relatively free from gross impurities. The doubly refractile crystals have a characteristic branched and crosslike appearance. Their ultimate shape depends somewhat on whether they are recovered

9. Rous, P., and Gilding, H. P.: J. Exper. Med. **51**:27, 1930.

10. Goldschmidt, S., and McGlone, B.: Am. J. Physiol. **109**:42, 1934.

11. Menkin, V.: J. Exper. Med. **64**:485, 1936.

as an acetone-dried residue or from an aqueous mother liquor. In either case, they tend to have a similar pattern, characterized by short dendrite-like projections arising on each side of a main shaft. The active crystals isolated from inflammatory exudates are soluble in water and dilute alcohol but are relatively insoluble in ether. An aqueous solution of the crystals shows a slight acid reaction (about p_H 6.5) although at times it displays a distinctly alkaline reaction to phenol red. The substance is heat stable. It yields a negative biuret reaction but a positive ninhydrin reaction, indicating thus the presence of free alpha-amino and carboxyl group. The Fehling and Molisch tests for carbohydrates are negative. I am engaged in studying the properties of this active crystalline substance, which is isolated in moderately large amounts from exudates and apparently also, but in reduced amounts, from normal blood serum, particularly if there has been any appreciable hemolysis.[12] The substance is capable of initiating the usual sequences of any inflammatory reaction with extreme rapidity, for within from twenty-five to thirty minutes after it has been cutaneously inoculated abundant migration of leukocytes through the capillary wall becomes conspicuous. In brief, having been able to crystallize and isolate from exudates a substance which appears to be responsible for the increase in capillary permeability in inflammation, my attention is now centered on an attempt to purify it completely and to identify it chemically. The present available evidence indicates that it is an intermediary product of protein catabolism, belonging probably to the group of polypeptides. Furthermore, studies that are being conducted on the further purification of the active substance do not preclude the definite possibility that the crystalline material finally recovered from exudates by the method described may well consist in a large measure of sodium chloride crystals to which there is adsorbed or at least intimately bound up the active crystalline nitrogenous substance. Chlorides are present in the material. Sodium determinations indicate that this element forms about 20 per cent of the total weight of the recovered substance, which is nevertheless nitrogenous. The nitrogen content of this material at its present state of purification averages about 2.3 per cent. It is precipitated by saturated ammonium sulfate. It is needless to state that the effects produced by the active material on the endothelial wall are not duplicated by

12. From nonhemolyzed blood serum a moderate amount of crystals may be recovered. In their pattern they resemble the crystals isolated from exudates. Yet the crystals from the serum are practically inactive as regards increasing capillary permeability. That they may represent a different material is further indicated by their distinctive alkaline reaction in contradistinction to the frequent acid reaction of the crystals isolated from exudates. The crystals obtained from nonhemolyzed blood serum exhibit also greater solubility in water than do those recovered from exudates.

sodium chloride alone.[12a] These studies are being pursued further and will form the subject of separate reports.[12b]

This substance recovered from exudates fails to exhibit histamine-like properties. This is indicated by the following considerations:

1. The capillaries of the rabbit's skin have been found by Morgan [13] to be relatively refractory to the action of histamine. Histamine dissolved in serum, saline solution or distilled water and injected into the dermis of a rabbit fails to exhibit the characteristic staining pattern displayed by an exudate or its active fractions. In the case of histamine either no dye penetrates into the treated cutaneous area or the skin is diffusely stained in a wide flarelike zone at the periphery of a large central unstained area. This staining pattern does not seem to be referable to the concentration of histamine injected, for practically identical results have been obtained when the amounts of histamine injected locally ranged from 0.5 to 10 mg.

2. The active crystalline material recovered from an exudate tends to decrease the tonus of an isolated loop of a guinea-pig's intestine, whereas histamine, as is well known, induces marked contraction of such a segment. Both cell-free exudate and the active crystalline substance isolated from it depress the tonus of isolated strips of intestine.

Corroborative evidence that histamine is antagonistic to the active principle from exudate was obtained on the addition of 1 mg. of histamine to 0.2 cc. of a potent exudate. The effect of the histamine prevailed and the areas on the dermis of the abdomen of the rabbit treated with this mixture were found to be refractory to the passage of dye from the circulating blood. According to recent observations of Barsoum and Gaddum,[14] if the addition of histamine to an unknown extract causes disappearance of the latter's original contractile effect on an isolated segment of intestine, there is good indication that the effect of the extract is due to histamine. For this reason an experiment was set up in which, after preliminary treatment of an isolated strip of a guinea-pig's intestine with the active concentrated dialysate of an

12a. Menkin, Valy: Proc. Soc. Exper. Biol. & Med. **36**:164, 1937.

12b. Studies on the further purification of the active crystalline nitrogeneous substance made since completion of this manuscript indicate that this substance can be largely dissociated from sodium chloride admixtures by prolonged extraction with butyl alcohol or by spontaneous crystallization from the acetone mother liquor at —20 C. The resulting active material consists of tiny rodlike or discrete aggregates of doubly refractile granules which on appropriate drying frequently appear as needle-shaped crystals. This further purified and active material is relatively insoluble in water; its nitrogen content averages 8.65 per cent, and it apparently belongs to the group of relatively simple polypeptides.

13. Morgan, J. R. E.: Arch. Path. **18**:516, 1934.

14. Barsoum, G. S., and Gaddum, J. H.: J. Physiol. **85**:1, 1935.

exudate, a solution of histamine was added. The usual depressing effect of the exudate or of its concentrated dialysate on the tonus of the intestine was immediately replaced by powerful tonic contractions showing that no state refractory to histamine had been induced by the preliminary treatment with the inflammatory exudate.

To conclude: The foregoing observations render it difficult to accept Sir Thomas Lewis' hypothesis that histamine or its closely related H substance is the primary cause of the increase in capillary permeability in inflammation. Evidence now available indicates that the increase is referable to the presence of a readily diffusible crystalline substance in the exudate. Although this substance has not as yet been identified chemically, the indications are against its being histamine or the closely related H substance.[14a]

The active crystalline substance recovered in particularly large quantities from exudates, unlike histamine,[13] plays a significant rôle in inducing the migration of leukocytes to the site of inflammation. I shall return to this question later. For the sake of convenience I have proposed the tentative name of "leukotaxine" for this active polypeptide-like substance recovered from exudates.

Duran-Reynals [15] described in some tissue extracts, particularly in testicular extracts, a spreading factor which facilitates the extension of various indicators, such as india ink, from the site of their cutaneous inoculation. He referred the phenomenon to an enhancement of the permeability of tissue by the organ extract employed. Recent observations indicate that the crystalline material recovered from exudates is probably not related to this spreading factor. The Duran-Reynals substance is relatively thermolabile and nondialyzable, whereas the active agent in exudates which increases the permeability of capillaries is both thermostable and dialyzable. My unpublished studies have shown that in testicular extracts both factors may be present, and that the spreading factor of Duran-Reynals may be dissociated from a heat-stable permeability factor which is apparently similar to, if not identical with, the one recovered from inflammatory exudates. It is to be noted that the permeability factor characteristic of exudates exists in blood serum, but biologic tests indicate that it is present there in distinctly lower concentrations than in exudates.[11] Unless there is considerable hemolysis, definitely fewer *active* crystals are recovered from blood serum than from cell-free exudate.

14a. The specific Zimmermann color reaction for histamine with cobalt nitrate and sodium hydroxide is negative for the active crystalline substance recoverable from exudates. This serves as additional evidence that the substance is not histamine.

15. Duran-Reynals, F.: J. Exper. Med. **50**:327, 1929.

Injury to capillaries and increase in plasma filtration seem to be closely linked with the subsequent phase of the inflammatory reaction. This phase may conveniently be termed the fixation or localization of the irritant, including bacteria, at the site of an acute inflammation. This phase is of special significance in an analysis of the rôle of inflammation in immunity. The earlier studies of Issayeff [16] on the increased resistance of guinea-pigs to intraperitoneal inoculation of bacteria when these animals had previously been given an injection of broth, foreign blood serum or physiologic solution of sodium chloride in the same area may be said to mark the beginning of studies on the capacity of the inflammatory reaction to inhibit or delay the spread of micro-organisms. Opie [17] demonstrated that a foreign protein injected into the dermis of an immunized animal is fixed at the site of injection. The contact of antigen and antibody at the site of injection causes an acute inflammatory reaction (the Arthus phenomenon). When, on the contrary, foreign proteins are injected into the dermis of normal animals, little, if any, inflammatory reaction ensues, and the proteins readily penetrate into the blood stream. Willis [18] studied the dissemination of tubercle bacilli from the site of cutaneous inoculation and showed that in reinfected guinea-pigs the spread of tubercle bacilli from the site of inoculation is retarded, whereas in normal animals the organisms pass readily to the regional lymph nodes. I [19] have demonstrated that various substances, including a vital dye (trypan blue), ferric chloride or colloidal iron, a foreign protein, graphite particles and bacteria, when injected into an acutely inflamed area are fixed in situ and fail to drain into the tributary lymphatics as readily as under normal circumstances. Furthermore, the observations indicated an interesting time relationship. Fixation tends to occur extremely early in inflammation induced by strong irritants, for instance, aleuronat or Staphylococcus aureus. The observations showed that the passage of trypan blue to the regional lymphatics was considerably delayed even when the dye was injected only thirty minutes after the subcutaneous introduction of aleuronat. This rapid walling off of the inflamed area allowed the relatively sluggish leukocytes a certain interval of time in which to assemble at the site of inflammation for phagocytosis and ultimate disposal of the irritant. It was also shown that these same substances when introduced into the circulating blood stream rapidly accumulate in the inflamed area. This is doubtless partly referable to the enhanced passage of

16. Issayeff: Ztschr. f. Hyg. u. Infectionskr. **16**:287, 1894.

17. Opie, E. L.: J. Exper. Med. **39**:659, 1924.

18. Willis, H. S.: Am. Rev. Tuberc. **11**:427 and 439, 1925.

19. Menkin, V.: J. Exper. Med. **51**:879, 1930; **52**:201, 1930; Arch. Int. Med. **48**:249, 1931.

fluid through the capillary wall, but it is due also to the inability of these substances to escape readily through the tributary lymphatics. The rate of dissemination or diffusion of various substances or of bacteria through the tributary lymphatics seems to be inversely related to the intensity of the local injury, i. e., within a given interval of time. The illuminating observations of Hudack and McMaster [20] readily demonstrated the prompt turnover of dyes through lymphatic channels from sites of comparatively mild injury. If the local lesion is characterized at an early stage by intense damage or if, in the course of time, the inflammatory reaction assumes sufficient intensity, lymphatic blockage is likely to be the result, as indicated by the inability of indicator substances to drain adequately to the tributary lymphatic vessels.

The concept that various substances introduced into the circulating blood stream rapidly accumulate and are fixed in situ in an acutely inflamed area perhaps offers an explanation for a number of pathologic processes. The frequent localization of bacteria from the blood stream in a locus minoris resistentiae after preliminary trauma or other injury to tissue is well known to pathologists and clinicians. Observations on the accumulation of bacteria from the blood stream in an inflamed area may explain the mechanism of this phenomenon in terms of increased permeability of capillaries with resulting accumulation and fixation of bacteria at the point of injury.[21] It is further conceivable that by the fixation of various materials in an area of injury the character or course of the inflammatory reaction may be altered. In this connection we have been able to demonstrate that repeated intravenous injections of ferric chloride into tuberculous rabbits are followed by deposition of some of the metal in tubercles.[22] Concomitantly with this accumulation the progress of the experimental disease is retarded as indicated by an appreciable increase in the period of survival and by a difference in the extent of the lesions in control and experimental rabbits. These original observations have recently received further substantiation by data on the number of viable bacilli recovered after culturing some of the involved organs of both control and experimental rabbits. Our studies have been carried on for a number of years and now involve the results of several independent series of experiments.[23] The clinical implications are obvious,[24] especially since the innocuousness of this iron salt in man has recently been pointed out.[24] It is conceivable also that one might

20. Hudack, S. S., and McMaster, P. D.: Proc. Soc. Exper. Biol. & Med. **29**: 944, 1932.

21. Menkin, V.: Lancet **1**:981, 1935.

22. Menkin, V., and Menkin, M. F.: J. Exper. Med. **53**:919, 1931.

23. Menkin, V.: J. Exper. Med. **55**:101, 1932; **60**:463, 1934; Proc. Soc. Exper. Biol. & Med. **34**:262, 1936.

24. Menkin, V.: Am. Rev. Tuberc. **35**:134, 1937.

find practical uses for a substance which by accumulating from the blood stream would enhance the roentgen appearance of various inflammatory lesions.

In several previous publications we have brought forward evidence indicating that the mechanism responsible for the fixation of various substances at the site of an acute inflammation seems to rest primarily on the establishment of an effective lymphatic blockade. This is brought about by two factors, the presence of each of which may vary in extent.[25]

The mechanical barrier which circumscribes the area of acute inflammation consists of coagulated plasma in tissue distended with edema, and if the reaction becomes sufficiently intense, there develops occlusion of the afferent lymphatic vessels by thrombi. It is quite likely that when the inflammatory reaction is fully developed other elements may participate in intensifying the retention of material in the injured area. In this connection leukocytes may, in the later phases of the inflammatory reaction, play some definite rôle through their phagocytizing properties. Inasmuch as I have previously demonstrated the prompt accumulation of foreign proteins from the circulation in inflamed foci, and since Fox[26] has recently obtained evidence suggesting that antibodies tend to localize in such areas, it is reasonable to suppose that in allergic or anaphylactic inflammation the mechanism of fixation is probably reinforced by the presence of specific antibodies. This view was foreshadowed by Opie[17] in his investigations on the mechanism of the Arthus phenomenon, and it was later developed further by Rich and McKee[27] in their interesting studies on the immune animal.

Careful analysis, however, of the mechanism involved in regard to the element of time or the threshold of fixation supports the view that lymphatic blockage constitutes the basic reaction but that, as I have often maintained, it may be reenforced by various factors. These, in turn, may be quite significant but are nevertheless considered secondary for the simple reason that they do not have to be present for the reaction of fixation to take place. As I have pointed out, the observations indicate that with some powerful irritants that cause considerable necrosis—for instance, aleuronat—fixation may occur as early as thirty minutes after introduction of the irritant, at a time when there is as yet a scarcity of leukocytes in the extracapillary spaces. Furthermore, microscopic studies at this period fail to reveal any trace of the foreign material in phagocytes. Yet the foreign substance is prevented from reaching the regional lymph nodes. Conversely, in studies

25. Menkin, V.: (*a*) J. Exper. Med. **53**:171, 1931; (*b*) Arch. Path. **12**:802, 1931; (*c*) J. Infect. Dis. **58**:81, 1936.

26. Fox, J. P.: J. Immunol. **31**:293, 1936.

27. Rich, A. R., and McKee, C. M.: Bull. Johns Hopkins Hosp. **54**:277, 1934.

of various types of acute nonallergic inflammatory reaction, I consistently failed to observe any sign of fixation of the tested material without some degree of occlusion of the afferent lymphatic vessels and generally the presence of a network of fibrin. The lymphatic channels were either completely or in part blocked by thrombi. The extent of fixation was usually well correlated with the extent of the deposits of fibrin in tissue distended with edema or with the degree of lymphatic thrombosis or with both these factors. In some types of acute inflammation, e. g., that associated with pneumococci of type I, in the rabbit skin, it was of interest to note the scarcity of fibrin in the extracapillary spaces, but the fixation of a vital dye in a cutaneous area inoculated with these micro-organisms was invariably correlated with the finding of thrombi in the draining lymphatic vessels. On the other hand, in inflammatory reactions induced by burning with hot water the retention of material was primarily correlated with the presence of fibrin in the extracapillary spaces rather than with conspicuous thrombosis of lymphatic vessels.[28] In conclusion, a combination of both factors or a prevalence of one or the other seems to be a requisite for fixation at the site of an acutely inflamed area.

The evidences for arriving at this conclusion have been described in detail elsewhere [29] and therefore will be restated here only in brief:

1. Morphologic examination substantiates the view that fixation may well be referable to a lymphatic blockade by fibrin and obstructive thrombi in lymphatic channels.

2. If mechanical obstruction plays an important rôle in fixation, substances which are unable to disseminate from the acutely inflamed area should, for the same reason, fail to enter it when they are injected at the periphery of the area. This is precisely what was found to occur when trypan blue or bacteria were injected at the periphery of an acutely inflamed focus. Burrows recently confirmed this experiment with india ink.[30] I [31] have had occasion to follow in the living frog, under the microscope, the diffusion of a dye from the peripheral site of its inoculation to the boundary of the inflamed area, where its further progress was blocked by a thrombus occluding a lymphatic channel.

3. By injecting concentrated urea, which dissolves fibrin, immediately after the injection of the irritant, it was possible to prevent any appreciable formation of obstructing thrombi in the tributary lymphatics and to inhibit fixation correspondingly. Urea had no other manifest

28. Menkin, V.: Proc. Soc. Exper. Biol. & Med. **30**:1069, 1933.

29. Menkin, V.: Am. J. M. Sc. **190**:583, 1935.

30. Burrows, H.: Some Factors in the Localization of Disease in the Body, London, Baillière, Tindall & Cox, 1932.

31. Menkin, V.: J. Exper. Med. **53**:179. 1931.

effect on the cytologic character of the exudate as revealed by microscopic examination.

These three types of distinct evidence render it likely that the mechanism of fixation in inflammation is primarily referable to a barrier in the form of thrombi in lymphatic vessels and coagulated plasma in tissue distended with edema. There is as yet no precise information on the relation of the increased passage of fluid from the capillaries to the lymph flow from an inflamed area. Pending the recording of such data, the finding of increased lymph flow from a main lymphatic trunk draining a large area of tissue unequally injured by the inflammatory irritant indicates, as would be expected, only an absolute increase in lymph flow.[32] In such an experiment one cannot preclude the possibility of a relative decrease in the lymph output when the total amount of plasma which has passed through the capillary walls is taken into consideration.[28] Inflammatory edema may in part be an index of the inability of a partially impaired lymphatic circulation to take care of the excessive passage of fluid from the circulating blood into the acutely inflamed tissue.

The foregoing observations on the mechanism of fixation have offered a means of studying a factor that may in large part account for differences in the invasive ability of various pyogenic organisms.

The intensity and rapidity with which an inflammatory irritant is circumscribed in an area of tissue vary with the type of irritant. The speed with which an irritant causes a region to be walled off by mechanical obstruction in the form of thrombi in lymphatic vessels or a fibrinous network or both is necessarily an important index in determining the ability of the irritant to disseminate into the circulating blood. This holds true if the irritant can readily drain through lymphatic vessels from the site of inoculation. That bacteria disseminate from the site of inoculation through such vessels has been frequently demonstrated. It follows from this that if bacteria are employed as inflammatory irritants some information may be obtained concerning their invasive capacities. In other words, can the behavior of various pyogenic organisms in tissues be related, at least in part, to their respective abilities of inducing an early inflammatory reaction at the site of inoculation which would tend to prevent, by the mechanism previously described, their dissemination to the tributary lymph nodes?

In observations described fully elsewhere [33] it was definitely shown that the difference in the invasive behavior of Staph. aureus, pneumococci and hemolytic streptococci was in large part referable to the differential degree of local injury induced by these micro-organisms. A cul-

32. Menkin.[28]

33. Menkin, V.: J. Exper. Med. **57**:977, 1933.

ture of Staph. aureus or its soluble toxin induces a prompt lymphatic blockade, as indicated by histologic examination at the site of its cutaneous inoculation, so that within about an hour an indicator dye fails to reach the tributary lymph nodes. In the case of hemolytic streptococci, it takes about two days subsequent to cutaneous inoculation before the local reaction becomes sufficiently intense to result in lymphatic blockade. These observations suggest a paradoxical interpretation. Staphylococci produce in general little systemic effect, owing to the intense local injurious reaction, which fixes them in situ. Streptococci produce profound generalized effects on the organism because the local reaction to their presence is comparatively mild. This fact allows them relatively free penetration to the essential organs for a considerable interval.

Dennis, who has confirmed these observations on the mechanism of invasiveness,[34] has recently advanced the idea that hemolytic streptococci have the specific capacity of inhibiting the formation of a circumscribing fibrinous barrier.[35] This investigator's conclusions are perhaps open to question inasmuch as the possibility of inactivating the irritant in vitro by mixing it with hemolytic streptococci is not precluded by his experiments. I,[36] in turn, have failed to alter the speed of fixation of injected aleuronat if hemolytic streptococci are inoculated into the same area of tissue either immediately following the injection of aleuronat or at intervals of from twenty to thirty minutes later.

We have recently obtained additional evidence indicating that the difference in the disseminating behavior of staphylococci and hemolytic streptococci is probably referable primarily to difference in the respective rates at which they induce local injury. We[37] have shown that often the severity of an inflammatory reaction can be graded by the extent of local disturbance in the intermediate carbohydrate metabolism. Lesions induced by Staph. aureus manifest considerably more glycolysis than do lesions of the same duration induced by hemolytic streptococci.[38] This chemical difference furnishes additional evidence that the invasiveness of each of these two micro-organisms bears an inverse relation to the intensity of its induced local lesion.

The observations indicate that the rapidity and the intensity of local fixation are factors in determining the invasiveness of an infectious micro-organism. Dissemination seems to bear a direct relationship to time and an inverse relationship to intensity of local injury. The

34. Dennis, E. W., and Berberian, D.: J. Exper. Med. **60**:581, 1934.

35. Dennis, E. W.: Proc. Soc. Exper. Biol. & Med. **35**:100, 1936.

36. Menkin, V.: Unpublished studies.

37. Menkin, V., and Warner, C. R.: Proc. Soc. Exper. Biol. & Med. **34**:594, 1936.

38. Menkin, V., and Warner, C. R.: Am. J. Path. **13**:25, 1937. Menkin, V.: Proc. Int. Cong. Microbiol., London, 1936, p. 144.

inflammatory reaction thus plays in problems of immunity an important rôle as a regulator of invasiveness.

The mechanism of the migration of leukocytes to an area of injury has not as yet been satisfactorily explained. The hypothesis that it is a matter of surface tension or that the difference in potential between normal and injured tissue favors the migration of negatively charged leukocytes [39] is still in part at least the result of inference. There is as yet little direct experimental observation to substantiate these views. I shall not take time to review the well known earlier investigations on the subject of chemotaxis, dating from the observations of Leber [40] in 1879 and those of Massart and Bordet [41] in 1891. It is interesting to note in this connection that the crystalline substance, leukotaxine, which I have isolated from inflammatory exudates not only initiates an almost immediate increase in capillary permeability when placed in contact with normal tissue but seems likewise to induce a surprisingly early aggregation and migration of leukocytes through the endothelial wall. It is of interest to determine whether this migration of white cells is referable to the substance per se or is secondary to changes initiated by the augmented permeability of the capillaries. The following experiment is suggestive: Turpentine was introduced intracutaneously into a rabbit, and almost immediately thereafter trypan blue was injected intravenously. The dye accumulated rapidly and in abundance in the treated area. About thirty-eight minutes after the introduction of the irritant, the involved area of the skin was excised and fixed in formaldehyde. Microscopic examination revealed numerous small vessels distended and engorged with red cells, but there was no evidence of any migration of leukocytes through the endothelial wall. In this respect the area was in marked contrast with two other cutaneous areas in the same animal treated for about as long a time with, in one instance, the crystalline material recovered from exudate and, in the other, that obtained from blood serum which had displayed evidence of hemolysis and, perhaps, light lipemia. Both these cutaneous areas revealed moderate to abundant leukocytic migration through the walls of the capillaries. This experiment suggests that enhancement of the permeability of capillaries by as strong an irritant as turpentine does not necessarily induce migration of leukocytes as rapidly as that observed in an area treated previously with the active crystalline material.

If the active crystalline material, leukotaxine, recovered from exudate by extraction with pyridine, acetone and butyl alcohol is taken up in distilled water or in saline solution and injected intracutaneously, within

39. Abramson, H. A.: J. Exper. Med. **46**:987 and 1003. 1927.

40. Leber, T.: Fortschr. d. Med. **6**:460, 1888.

41. Massart, J., and Bordet, C.: Ann. Inst. Pasteur **5**:417, 1891.

from seventy-five to thirty minutes, the capillary lumens are found literally crowded with polymorphonuclear leukocytes, adhering closely to the wall and actively migrating through the endothelium. However, as mentioned previously, in the same animal, lesions of comparative duration have been induced with a crystalline material which was relatively inactive as regards its effect on the permeability of the capillaries. This substance was obtained by extracting it from clear blood serum containing no vestige of hemolysis. This product by itself, as well as distilled water or saline solution, fails to stimulate appreciable migration of leukocytes through the capillary wall. It is also to be noted that leukotaxine has been found to be positively chemotactic. The unusual rapidity of the extensive migration of leukocytes in the presence of the crystalline substance isolated in abundance from exudates, also sometimes from blood serum containing evidences of hemolyzed red cells, suggests as a hypothesis the possibility that injured tissue liberates a diffusible crystalline substance, apparently a polypeptide, capable of initiating the various features of the inflammatory reaction.[42] My studies of the details of this problem will form the subject of a subsequent report.

For many years it has been known that the cytologic sequence in acute inflammation is characterized in the earliest stages by active emigration of polymorphonuclear leukocytes. After a time this is followed by infiltration of mononuclear phagocytes or macrophages. In acute inflammation the polymorphonuclear cells that leave the circulating blood stream form the chief cellular constituents of the early exudate. The mononuclear phagocytes or macrophages increase in number in the later stages. The orderly cytologic sequence in the inflammatory reaction was first pointed out by Borrel [43] and then by Durham [44] and Beattie [45] over forty years ago. This sequence seems to characterize the majority of acute inflammatory reactions caused by bacteria or by chemical irritants.

No adequate explanation had been offered for this fundamental process. The earlier basic work of several investigators, particularly that of Opie,[46] on the presence of proteolytic enzymes in leukocytes has been particularly instructive. Müller [47] and Opie [48] had described

42. Such a hypothesis does not preclude the possibility that certain irritants may contain the active factor. Hence the concentration of the material which is liberated from cells during injury may be augmented by direct introduction of the irritant.

43. Borrel, A.: Ann. Inst. Pasteur **7**:593, 1893.

44. Durham, H. E.: J. Path. & Bact. **4**:338, 1897.

45. Beattie, J. M.: J. Path. & Bact. **8**:129, 1903.

46. Opie, E. L.: J. Exper. Med. **8**:410, 1906.

47. Müller, F., cited by Kossel, H.: Ztschr. f. klin. Med. **13**:149, 1888.

48. Opie, E. L.: Arch. Int. Med. **5**:541. 1910.

an enzyme within polymorphonuclear cells that was active in a neutral or slightly alkaline medium. This enzyme was termed "leukoprotease." [4] Macrophages or mononuclear phagocytes contain an enzyme active in a weakly acid medium, to which Opie [48] gave the name "lymphoprotease." It occurred to us that there may be a parallelism between the concentration of hydrogen ions in the fluid medium and the p_H which is optimal for the action of the intracellular enzyme of the predominating type of phagocyte. It seemed conceivable that prior to phagocytosis by a given type of leukocyte the particles in an inflammatory exudate may tend to have on their surfaces a concentration of hydrogen ions approximating that of the intracellular proteolytic enzyme capable of digesting them. If this assumption was correct, one might expect that the inflammatory exudate in which such particles are immersed would gradually become more acid with the shift from polymorphonuclear to mononuclear phagocytes. Lord [49] in his studies of the pneumonic lung had concluded that during the course of the disease a gradual increase in concentration of hydrogen ions in the exudate probably occurred. Schade and his co-workers [50] reported that pus from acute abscesses had a p_H ranging from 5.95 to 6.50. The question arose, therefore, whether or not there exists a correlation or perhaps an interdependence between the p_H of the medium and the cytologic picture during an acute inflammatory reaction.

A great number of observations were made on pleural exudates obtained from dogs. Both p_H measurements and examinations of the cytologic picture were made from day to day. In the severer types of inflammation it was found that an increase in the concentration of hydrogen ions occurred within from two to four days; i. e., the p_H fell from about 7.4 or 7.3 to 6.8 or 6.7 and sometimes even lower.[51] The development of acidosis was purely local; the p_H of the blood was essentially unaltered. Concomitantly with this decrease in p_H, the cellular picture shifted from one in which polymorphonuclear cells predominated to one characterized almost exclusively by the presence of macrophages. If the p_H fell below 6.8 or 6.7, all types of leukocytes were found to be injured, and frank pus ensued. Evidence was obtained suggesting definite interdependence between the p_H and the cytologic picture in acute inflammation. For instance, if the course of the reaction was mild and acidosis failed to develop in the exudate, polymorphonuclear cells predominated throughout. Furthermore, some experiments indicated that the changes in p_H preceded rather than fol-

49. Lord, F. T.: J. Exper. Med. **30**:379, 1919.

50. Schade, H.; Neukirch, P., and Halpert, A.: Ztschr. f. d. ges. exper. Med. **24**:11, 1921.

51. Menkin, V.: Am. J. Path. **10**:193, 1934.

lowed the cytologic shift. The data strongly suggest that the concentration of hydrogen ions conditions the cytologic picture and that the type of cell to be expected at a given time can be predicted from the p_H measurements and vice versa with a fair degree of accuracy. Below p_H 7 the polymorphonuclear leukocytes seem unable to survive, and this holds true of the macrophages as well, but only when the p_H reaches a level below 6.7 or thereabouts. The possible implications of these findings in regard to facilitating a clearer understanding of the histologic manifestations of various lesions are obvious.

These observations indicate that information leading to the elucidation of the mechanism of local acidosis would be of aid in an analysis of the factors determining the type of cellular response in inflammation. Previous studies had demonstrated that in acute inflammation there is impairment of local circulation, as evidenced by lymphatic blockade and, in the later stages of the acute inflammatory reaction, by considerable thrombosis of capillaries. As the reaction intensifies, the area of inflammation becomes shunted off from the rest of the organism; i. e., it develops its own p_H, its own local circulation and its own metabolism. It is conceivable that the impairment of the local circulation of lymph and blood in acutely injured tissues may tend to promote a state of relative anoxemia, especially since Gessler [52] has shown that in an inflamed area consumption of oxygen and metabolism are increased. With interference in normal oxidative reactions, glycolytic respiration of an anaerobic type may result. This would manifest itself in conversion of sugar to lactic acid. If glycolysis should become accelerated with no augmentation in the available alkali reserve, uncompensated acidosis would result in the inflamed tissue. This seems to be precisely the course of events.[38]

With the gradual development of acidosis in an area of inflammation, the volume per cent of carbon dioxide in the cell-free exudate tends to fall correspondingly. Analysis of the blood serum, however, reveals no appreciable change in its carbon dioxide content. Studies of the total carbon dioxide content of exudate indicate that with progress of the inflammatory reaction there results a local depletion of the alkali reserve; the p_H falls, and the polymorphonuclear cells are replaced by macrophages. If a frankly purulent exudate develops with a p_H of 6.5 or below, the carbon dioxide may fall to about 8 volumes per cent or less. The leukocytes in such viscous suppurative material are for the most part swollen and degenerated and are identified, if at all, only with the greatest difficulty. The depletion of the alkali reserve adequately accounts for the development of an uncompensated acidosis at the site of inflammation. As mentioned previously, the acid produced is the result

52. Gessler, H.: Arch. f. exper. Path. u. Pharmakol. **163**:456, 1932.

of local disturbance in carbohydrate metabolism. There is augmentation of glycolysis as the reaction increases in severity. With the fall in sugar there is marked rise in the lactic acid of the exudate. The p_H falls, and the cytologic picture shifts accordingly.[38] The observations indicate, apparently, that the cytologic picture in acute inflammation is conditioned by the hydrogen ion concentration, which in turn depends on the local disturbance in carbohydrate metabolism and on the depletion of the alkali reserve.

SUMMARY AND CONCLUSIONS

I have, in this discussion, attempted to point out what, in my opinion, are some of the significant features of the local inflammatory reaction in its relation to immunity. An analysis of the salient sequences reveals an interdependence of dynamic phenomena, all of which finally tend to dispose of the irritant and to induce reparative processes. These features may be summarized as follows:

The initial increase in plasma filtration occurring in inflammatory conditions seems to be primarily referable to an increase in the intracapillary pressure and in the permeability of the minute vessels. There is evidence that the increase in permeability of the endothelial wall is referable to a liberation from injured tissue of a diffusible crystalline substance other than histamine. This factor can be isolated from exudates and recovered in detectable quantities.[12a] It is capable of inducing pronounced seepage through the capillary wall. Passage of plasma proteins, including fibrinogen, into the injured part is thus favored at a very early stage of the reaction. Prompt coagulation of the plasma and formation of obstructive thrombi in the afferent lymphatics circumscribe the area of injury, inhibiting the dissemination of the irritant. Thus the primary mechanism of fixation in inflammation, which under some circumstances may be reenforced by various secondary factors, plays a definite rôle in immunity. The prompt early walling off of the irritant allows the leukocytes time to collect at the site of inflammation for phagocytosis. The rapidity and intensity of the fixation are largely a function of the irritant. Irritants that cause necrosis induce an extremely prompt local reaction inhibiting their spread. The reverse is true of weak irritants. Observations on the behavior of various pyogenic micro-organisms indicate the rôle of the inflammatory reaction in regulating the rapidity of invasiveness and therefore the significance of this reaction in grading the immunity or resistance of the host. In brief, the dissemination of micro-organisms seems, at least during a given interval, to be inversely related to the intensity of the local injury which they cause.

There is definite evidence that the migration of polymorphonuclear leukocytes in inflammation is related to the liberation of the

nitrogenous crystalline substance which can be recovered from exudates and which induces initially an increase in the permeability of capillaries. The available evidences indicate that this substance probably belongs to the group of polypeptides. It possibly represents the result of an interference with normal protein catabolism in an area of injury. The tentative name "leukotaxine" is proposed for this active substance which is per se capable of rapidly reproducing the basic sequences of the inflammatory reaction.

Finally the disturbance in local circulation which doubtless occurs at the site of inflammation as a result of enhanced capillary filtration, lymphatic blockade and subsequent capillary thrombosis tends, by shunting off the injured area, to favor development of local acidosis. This results from a disturbance of the local intermediary carbohydrate metabolism, as evidenced by increased glycolysis, and from a depletion of the alkali reserve. At a given time the prevailing concentration of hydrogen ions in the exudate seems to play a significant rôle in the determination of the cytologic picture. Observations indicate that the marked fall in the p_H is associated with an overwhelming lethal effect on all types of leukocytes, and that frank suppuration is the result.

Notes and News

American Documentation Institute.—The objective of this new institute, which is located in Washington, D. C., is to foster the development of all phases of documentation, particularly photomicrographic duplication and its ramifications, in the fields of physical, natural, social and historical sciences and in the general sphere of libraries and information services. In cooperation with Washington libraries, it will operate bibliofilm services, mainly in substitution for lending; it will also operate auxiliary publication services not only by means of microfilm but by other methods of duplication.

Research in the Cancer Field.—The Belgian Mining Association has awarded 50,000 Belgian francs and 50 mg. of radium to E. L. Kenneway and J. W. Cook, British investigators, as a prize for their work on cancer.

The Finney-Howell Research Foundation for the study of cancer is provided for in the will of Dr. George Walker, head of the outpatient surgical department of the Johns Hopkins Hospital. The purpose of the foundation is to provide fellowships with annual stipends of $2,000 each for the study of cancer. Special support may be given to work of fellows. The principal, said to be $300,000, must be expended as indicated within ten years. Fellowships may be awarded to workers in any part of the world.

The International Cancer Research Foundation has made a grant of $6,000 toward the study by Temple Fay in the medical school of Temple University, Philadelphia, of the relationship between body segmental temperatures and the incidence of cancer.

Abstracts from Current Literature

To Save Space the Original Titles of Abstracted Articles Sometimes Are Shortened

Experimental Pathology and Pathologic Physiology

Effect of Stellate Ganglionectomy on the Cardiac Function of Intact Dogs. W. V. Cox and H. F. Robertson, Am. Heart J. **12**:285, 1936.

Twenty dogs, carefully trained and tested during resting and during exercise for cardiac rate, respiratory rate and blood pressure, and ten for cardiac output, were subjected to coronary ligations as similar in nature as possible. Prior to the ligations, half the dogs were subjected to bilateral excision of the stellate ganglion, at which time at least several of the upper dorsal ganglions were also removed. The dogs from which the stellate ganglions had been removed were not affected by coronary ligation, as judged by the aforementioned criteria of cardiac function. With this procedure there was no change in the cardiac output or rate, respiratory rate or blood pressure. Only one of the ten dogs died of acute cardiac failure. At autopsy the infarcts in the hearts of these dogs were all smaller than those in the hearts of similar size in the other group of dogs. The dogs with stellate ganglions intact were much more affected by coronary ligation. There was no great difference between the two groups in pulse, respiration or blood pressure, but the resting cardiac output in this group became elevated considerably after coronary ligation and remained elevated. Five of the ten dogs died of acute cardiac failure typical of that seen in human beings with coronary disease, and the hearts of this group all exhibited larger infarcts than the hearts of similar size of the other group.

From the Authors' Summary.

Relation of Diet to the Occurrence of Gastric Lesions in the Rat. E. L. Howes and P. J. Vivier, Am. J. Path. **12**:689, 1936.

Hyperplasia, hyperkeratinization and ulceration of the squamous epithelium of the rumen of the rat's stomach result from an inadequacy in the diet. Similar lesions without keratinization occur in the glandular epithelium as well. The importance of these lesions lies in the relation of dietary insufficiencies to hyperplasia of tissue. Young rats are more sensitive to inadequacy of diet than are adult rats. Adult rats on the same diet must be starved every other day in order to acquire the lesions in the same length of time. An adequate intake of whole yeast prevents the formation of the lesions in both young and adult rats. Additional amounts of vitamin-free casein, cod liver oil or other forms of vitamin A do not prevent the formation of the lesions. Ingestion of feces prevents their occurrence.

From the Authors' Summary.

Experiments on the Theory of Osteogenesis. C. B. Huggins, H. R. McCarroll and B. H. Blocksom Jr., Arch. Surg. **32**:915, 1936.

Transplantation of bone that has been hydrolyzed in strong alkali to destroy the organic elements to the abdominal muscles or to the skull and ribs to replace defects did not stimulate the formation of new bone. Transplantation of deciduous teeth to the abdominal muscles led to the formation of bone in these teeth. Prior boiling of the transplant completely inhibited the formation of bone. Epithelium of the urinary bladder transplanted to the abdominal wall of the rat or of the guinea-pig led to the formation of cysts and production of bone. In the dog, epithelium of the urinary bladder transplanted into the spleen did not lead to

formation of bone unless connective tissue capable of ossification was transplanted with it. Transplantation to the surface of the spleen led to the formation of a small amount of new bone in several cases. The peritoneum and adjacent fibroblasts, including the omentum, easily ossified under the epithelial stimulus. This led to the conclusion that the subperitoneal fibroblasts in the outer coat of the bladder differ from the fibroblasts adjacent to the lining epithelium of this structure in that the former ossify when in contact with bladder epithelium while the latter do not. The defense against the ossifying action of the epithelium of the urinary bladder thus is topographically confined to the inside of the bladder and is lacking in the outside coverings of this viscus.

FROM THE AUTHORS' SUMMARY.

RESPONSE OF PERITONEAL TISSUE TO CERTAIN INJECTED DUSTS. J. W. MILLER and R. R. SAYERS, Pub. Health Rep. **51**:1677, 1936.

The tissue of the peritoneal cavity responds actively to a dust introduced as a foreign body. The reaction to various dusts fall into three groups; namely, those of absorption, those of proliferation and those of inertness. The responses may be used as a basis for the classification of industrial dusts. In the experiments described in this article animals were kept on test for as long as twelve months, but the response is sufficiently well marked in three months to determine the type of reaction, and often conclusions can be reached in one month, particularly if the reaction is one of absorption or one of proliferation. The reaction elicited by each dust was constant and uniform in all the animals into which the dust was injected.

The results obtained by the method used seem to indicate that some relationship exists between the type of reaction produced in the peritoneal tissue by a given dust and the ability of this dust to produce a characteristic type of pneumonoconiosis. Thus, an absorptive reaction may indicate that the dust is relatively harmless, while a proliferative reaction, the characteristic response to pure silica (quartz), may be associated with definite ability to produce nodular pulmonary fibrosis.

Interpretation of the significance of the dusts causing inert reactions is more difficult, but it appears logical to assume that dusts which show a tendency to remain in the tissues should be considered as potentially harmful, though not as dangerous as those causing a proliferative response. It is likewise logical to assume, and it has been proved to some extent in this laboratory, that silica mixed with an inert dust causes a modified proliferative reaction.

The results from application of this biologic method of classification have in a number of instances been correlated with clinical observations and industrial surveys, and it has been shown to be quite possible to use the method to determine the pneumonoconiotic potentialities of a dust in a relatively short time, usually two months.

FROM THE AUTHORS' CONCLUSIONS.

EFFECT OF DEFICIENT DIET, WITH AND WITHOUT EXTRACTION OF TEETH, ON THE DENTITION OF THE GUINEA-PIG. S. FORSHUFVUD, Ann. d'anat. path. **12**:279, 1936.

In 125 guinea-pigs fed various diets deficient in calcium and vitamins, Forshufvud found that it was the shift from the normal to the deficient diet, not the latter diet, which was responsible for the development of caries. By experimental extraction of teeth he came to the additional conclusion that the teeth are not independent, but that each tooth is intimately related to the others and to the dental alveoli, and that they are all dependent on the general metabolism.

PERRY J. MELNICK.

EXPERIMENTAL FIBROUS OSTEODYSTROPHY. T. PERRAS, Virchows Arch. f. path Anat. **296**:212, 1935.

Young rats received daily subcutaneous injections of parathyroid extract in gradually increasing doses for average periods of twenty-five days. One group of the animals was maintained on a normal synthetic diet. Another group received this diet plus an excess of vitamin D. A third group received the basal diet with a deficiency of vitamin D. The fourth group was kept on the basal diet made poor in both vitamin D and calcium. Osseous changes identical with those of human fibrous osteodystrophy developed in the animals on a normal diet and parathyroid hormone. The process began as an acute resorption of bone, apparently mediated through the presence of many osteoclasts. This was followed by the appearance of numerous osteoblasts and the formation of uncalcified osteoid tissue and by fibrosis of the marrow. Excess of vitamin D led to partial neutralization of the opposing effects of the hormone and the vitamin, although bone changes like those of early osteodystrophia developed. Deficiency of vitamin D led to increased reactivity of the animals to the hormone. When there was a deficiency of both the vitamin and the hormone, marked osteoporosis occurred, in part hyperostotic and in part hypostotic. Cysts and giant cell granulomas or "brown tumors" were not observed in the experimental animals, presumably because of the relatively short duration of the experiments.

O. T. SCHULTZ.

EFFECTS OF AMINO-ACIDS AND OTHER BIOLOGIC MATERIALS ON DEVELOPMENT IN THE CHICK EMBRYO. E. JENEY and E. TÖRÖ, Virchows Arch. f. path. Anat. **296**:471, 1935.

After forty hours' incubation of the hen's egg a minute opening was made through the shell, and a drop of the material to be investigated was injected in such a manner that the material came in contact with the surface of the developing embryo. The opening was sealed, and incubation was continued for forty-six hours. In control experiments an opening was made into the shell and a drop of Tyrode solution injected. Embryonic development was accelerated by arginine, valine, leucine, homologous hemoglobin, globin solution, liver extract and in some instances the saliva of normal nonsmokers. Embryonic development was retarded by amino-acetic acid, cysteine, cystine, isoleucine, serine, cadaverine, bilirubin and the saliva of persons with pernicious anemia. Death of the embryos resulted with ornithine, creatinine, tryptophan and in some instances with the saliva of persons suffering from pernicious anemia. The formation of blood islands and blood vessels was stimulated by homologous hemoglobin, globin solution, liver extract, arginine, valine and in some instances the saliva of normal persons.

O. T. SCHULTZ.

HYPERERGIC INFLAMMATION ON A TUBERCULOUS BASIS. F. ALTMANN and L. GERZNER, Virchows Arch. f. path. Anat. **296**:480, 1935.

Rheumatism is defined as an allergic disease characterized by a hyperergic inflammatory reaction on the part of the blood vessels and connective tissue. Whether the antigen that sensitizes the organism and mediates the hyperergic reaction is a specific micro-organism remains doubtful but is unlikely in view of the work of Reitter and Löwenstein and of Coronini and Popper, who were able to cultivate tubercle bacilli in cases of rheumatism. These findings and the rôle of the tonsils or pharynx in initiating the rheumatic attack led to the experiments reported here. The object was to determine whether a hyperergic inflammatory reaction might be produced experimentally by means of tubercle bacilli. A human strain of weak virulence for the rabbit was used. In one series the animals were sensitized by an intravenous dose of the bacilli, the dosage being small in order to minimize the possibility of specific tuberculous lesions. Twenty-eight days later the activating dose of the suspension of tubercle bacilli was injected into

the peritonsillar tissues of each side, the various tissues being examined histologically. In the blood vessels, joints and striped musculature there were observed inflammatory changes of hyperergic type, such as occur in human rheumatism. Focal inflammatory lesions were seen also in the myocardium, but the frequent occurrence of focal lymphocytic infiltration in the myocardium of rabbits is noted. The peritonsillar tissues revealed no reaction; the authors claim that the same is true of human rheumatism, in spite of the evident participation of the tonsils in the initiation of the process. In a second series of rabbits the sensitizing dose of tubercle bacilli was injected into the peritonsillar tissues, and twenty-eight days later the activating dose was injected intravenously. In this series only the myocardium revealed subacute inflammatory reaction. Although the experiments seem to uphold the thesis that the tubercle bacilli may be the sensitizing agent in rheumatic disease, it is to be noted that the number of animals was small, only five in each series.

O. T. SCHULTZ.

EXPERIMENTAL ATHEROSCLEROSIS ON A HYPERERGIC BASIS. H. SCHMITT, Virchows Arch. f. path. Anat. **296**:603, 1936.

The occurrence of atherosclerosis of the aorta and coronary arteries at an early age in persons who have previously had an attack of acute articular rheumatism has led Klinge and others to assert that the atherosclerotic process is an end-stage in a vessel previously damaged by the acute hyperergic inflammatory reaction which is held to be characteristic of rheumatic disease. In Schmitt's work control experiments established that hyperergic inflammation of the aorta can be produced in sensitized rabbits and that atherosclerosis of the aorta can be brought about in normal rabbits by feeding them cholesterol. The animals were sensitized with swine serum. In one series they were fed cholesterol during the course of the sensitization, and in another series cholesterol feeding was begun after the sensitization and the activating injection of serum. The activating dose of serum mediates a hyperergic arterial reaction similar to that seen in rheumatism. In sensitized animals lipoid infiltration and atherosclerosis could be brought about by much smaller amounts of cholesterol than were required in normal animals. The author holds that his results established the relation of atherosclerosis as a secondary infiltrative process in a vessel previously damaged by the hyperergic reaction of acute rheumatic disease.

O. T. SCHULTZ.

INTRACUTANEOUS RESORPTION OF FATS AND LIPOIDS. H. REISS, Virchows Arch. f. path. Anat. **296**:627, 1936.

A variety of fats and lipoid substances were injected into the skin for the purpose of determining a possible rôle of fat resorption in the pathogenesis of inflammatory disease of the skin. The substances used were cholesterol in emulsion and in concentrated solution in paraffin oil, hydrous wool fat in the melted state, stearic acid in 50 per cent solution in paraffin oil, oil in the form of glycerin ester of oleic acid, and neutral soap. The material in quantities of from 0.1 to 0.3 cc. was injected into the skin of the lateral gluteal region. A single injection and two injections at an interval of from three to four days were used. The skin was excised after from three to four days and studied microscopically. The earliest change was a splitting of the substance from its solvent. The material was dispersed in a finely granular state, taken up by phagocytes, which the author terms "lipophore cells," and transported to the epidermis. Free cholesterol was most readily disposed of; stearic acid was dispersed and phagocytosed with greatest difficulty. The injected substances caused an abnormality of hornification in the form of parakeratosis and dyskeratosis. The more complex fatty substances evoked greater inflammatory reaction than the simpler lipoid materials. The inflammatory reaction was similar to that seen in certain inflammatory diseases of the skin.

O. T. SCHULTZ.

Pathologic Anatomy

So-Called Atrophy of the Adrenal Cortex with Intranuclear Inclusions. H. A. Weiner, Am. J. Path. **12**:411, 1936.

A case of "atrophy" of the adrenal glands in a 53 year old woman is reported. The apparently sudden onset after a slight trauma and the rapid clinical course are noteworthy. Intranuclear inclusions were found in the cortical cells of the adrenal glands. Together with other characteristics noted, these may offer possibly another etiologic interpretation.

From the Author's Summary.

Newly Formed Lymph Vessels in Carcinomatous Peritoneal Implants. J. A. Sampson, Am. J. Path. **12**:437, 1936.

Cancer cells that escape into the peritoneal cavity frequently cause reactions of its serosal lining leading to an implantation of some of these cells on the surface of the peritoneum. The most important of these reactions for the study of the problem presented in this paper is the formation of various types of granulation tissue, in which the cancer cells become enmeshed. Cancer cells, however, are not necessarily found in all portions of this tissue. This granulation tissue provides the stroma for many peritoneal implants. In all parts of this granulation tissue spaces or vessels are found which are either empty or contain a few lymphocytes. They are lined by endothelium-like cells, usually accompany newly formed blood vessels, appear to be continuous when followed in serial sections and, in some instances, can be shown to take origin from preexisting lymphatics in the underlying peritoneum. In other instances, however, for reasons which have been given, these spaces cannot be detected or, if evident, their continuity with preexisting lymphatics cannot be determined. They are found in all types of granulation tissue in patients with peritoneal carcinomatosis. They occur in the low as well as in the polypoid masses of this tissue but are more readily seen in the polypoid group. The presence of dilated lymph vessels in low granulation tissue of the serosa in which clumps of cancer cells may become embedded deserves special attention. Some of these vessels apparently are preexisting and have expanded in the new-formed tissue. In other instances the tips of preexisting vessels apparently grow outward and form blebs or even small cysts in the granulation tissue. These dilated lymph vessels may furnish a ready portal of entry into the lymphatic circulation for the carcinoma embedded in the tissues about them.

From the Author's Summary.

Lesions of the Cardiac Valve Rings in Rheumatic Fever. L. Gross and C. K. Friedberg, Am. J. Path. **12**:469, 1936.

The lesions in the valve rings and intervalvular fibrosa in ninety-seven cases of rheumatic fever have been described. The cases have been divided into six clinical groups which represent various courses taken by this disease. It has been shown that each group presents certain general gross and microscopic features that bear relation to the clinical grouping. New macroscopic and microscopic data are presented on the development of the rheumatic lesions in the valve rings, and their significance with regard to the spread of the rheumatic infection to and from these sites is discussed. It is shown that the findings herein presented, as well as those previously reported, are of value in elucidating the pathogenesis of other cardiac lesions. Inasmuch as the valve ring constitutes the proximal portion of the valve leaflet, the lesions of the ring are of considerable significance in studying the development of rheumatic valvulitis. A description is also given of the changes that take place in nonrheumatic valve rings during the first eight decades of life.

From the Authors' Summary.

INTRANUCLEAR INCLUSIONS IN THE KIDNEY AND LIVER CAUSED BY LEAD POISONING. S. S. BLACKMAN JR., Bull. Johns Hopkins Hosp. **58**:384, 1936.

Intranuclear acidophilic inclusions were found in the tubular epithelium of the kidneys and in the cells of the liver in twenty-one cases of lead poisoning in children, and similar inclusions were reproduced in the kidneys of guinea-pigs, mice and rats by adding lead to their diet. The inclusions in the livers and kidneys of children and those produced experimentally in animals were variable in size and shape. Many of them were quite large and were round, smooth and homogeneous in appearance. Some were plastic, assuming the shapes of the distorted nuclei in which they occurred. Some of the nuclei contained many small granular and droplike inclusions. Like the intranuclear inclusions of virus diseases, the majority of the inclusions studied were stained by dyes, such as eosin and phloxine, and they gave a negative staining reaction to thymonucleic acid. It is probable that the inclusions described represent accumulations in damaged cells of the acidophilic material which is present in smaller amounts in normal cells.

FROM THE AUTHOR'S SUMMARY.

CHRONIC DESTRUCTION OF THE KIDNEY AND PARATHYROID HYPERPLASIA. H. A. MAGNUS and R. B. SCOTT, J. Path. & Bact. **42**:665, 1936.

A case of chronic nephritis with hyperplasia of the parathyroid glands and pathologic calcification is recorded. Evidence is brought forward to show that the renal lesion was the primary change. FROM THE AUTHORS' SUMMARY.

DIFFERENTIAL CELL COUNTS OF THE PITUITARY GLAND IN HYPERTENSION AND ENDOCRINE DISTURBANCES. F. HAWKING, J. Path. & Bact. **42**:689, 1936.

The pituitary was studied in various diseases by making differential counts of the cells according to the method of Rasmussen. In essential hypertension (twelve cases) the percentage of basophilic cells in the anterior lobe was found to be high in some but not in all cases. It is concluded that this change is not of etiologic importance, although it may be a secondary phenomena. In diabetes mellitus (six cases) no consistent deviation from the normal could be discovered. In hyperthyroidism or exophthalmic goiter (six cases) the total weight of the gland was reduced but not out of proportion to the total loss of weight for the whole body; the percentage of acidophilic cells was normal or diminished; that of basophilic cells, normal or raised. There was no consistent histologic evidence that the pituitary plays a dominant rôle in this condition. In Addison's disease (two cases) the percentage of acidophilic cells was somewhat diminished, while that of basophilic cells was greatly reduced; this confirms the conclusion of previous observers that there is a specific relationship between the adrenal cortex and the basophilic cells of the anterior lobe of the pituitary. In six of the twelve cases of essential hypertension there was moderate invasion of the posterior lobe of the pituitary by basophilic cells; but this was present also in two of three pituitaries from "normal" persons and in several from persons with other pathologic conditions. It is concluded that this basophilic invasion has no pathologic significance.

FROM THE AUTHOR'S SUMMARY.

INCREASE IN THE DIAMETER OF THE AORTA WITH AGE. J. B. CLELAND, M. J. Australia **1**:818, 1936.

While making postmortem examinations of young persons, Cleland noticed that the diameter of the aorta of the young person is less than that of the older person. He took measurements of the diameter of the aorta just above the aortic valve and an inch or so above the diaphragm, to see whether there was any regular increase in size with age. He found that there is a regular increase in the diameter of the aorta with advancing years. The aortas of 227 males and 147 females were measured. In males below the age of 21 the average measurement above the

valve was 1.7 cm., and the average above the diaphragm was 1.2 cm. In those between the ages of 21 and 30 the average measurements were 1.82 and 1.36 cm., respectively; between 30 and 40, 2.05 and 1.39 cm.; between 40 and 50, 2.21 and 1.6 cm., and so on; those over 70 years of age showed average values of 2.75 and 1.92 cm., and those over 80, 3.15 and 2.22 cm. The measurements in females showed slightly lower values, but here, too, an increase could be noted with the advance in years.

THE MYONEURAL JUNCTION, OR MOTOR PLATE, IN ITS NORMAL STATE AND IN CERTAIN PATHOLOGIC CONDITIONS. R. NOEL and B. POMME, Ann. d'anat. path. **12**:621, 1935.

In a detailed and lengthy histologic study Noel and Pomme describe the normal myoneural junctions and the changes found in them in the following conditions: postencephalitic parkinsonism, paralysis following serum therapy, progressive muscular atrophy, pseudohypertrophic muscular dystrophy, and acute anterior poliomyelitis. They conclude that the motor end-plate is not a muscle structure but is an exposed nerve fiber with its constituent elements spread out on the surface of the muscle fiber, composing a highly specialized synaptic zone. In the various diseases mentioned, changes take place either in the constituents of the motor plate alone or in these together with the muscle fibers. [These studies are of special interest in view of the recently discovered neurohumoral substances.]

PERRY J. MELNICK.

PULMONARY INFARCTS OF EMBOLIC ORIGIN. J. DELARUE, L. JUSTIN-BESANÇON and P. BARDIN, Ann. d'anat. path. **12**:681, 1935.

Histologic studies were made of pulmonary infarcts produced in dogs by intravenously injected emboli. These studies led the authors to believe that such infarcts do not consist simply of edema and hemorrhage by diapedesis resulting from mechanical interference with the circulation but that they represent an acute reactive inflammatory process. Almost identical changes in the lungs were produced in dogs by stimulating the sympathetic trunks in various ways or by cutting the vagus. They conclude that the process results from a sudden upset of the equilibrium of the vasomotor nerve supply.

PERRY J. MELNICK.

A CASE OF BALANTIDIASIS IN MAN FOLLOWED BY GRANULOMATOUS MYOCARDITIS. P. SIDOROV, Ann. d'anat. path. **12**:711, 1935.

In a case of ulcerative colitis in a 53 year old man caused by Balantidium coli, histologic sections of the colon revealed many amebas throughout the wall and also in the lumens of the smaller blood vessels. In addition, granulomatous myocarditis was present, with the amebas demonstrable in both the myocardium and the epicardium. This is the only case of such a myocarditis recorded in the literature.

PERRY J. MELNICK.

TERMINAL LESIONS OF THE TUBERCULOUS LUNG. I. AMEUILLE and M. DELHOMME, Ann. d'anat. path. **12**:745, 1935.

The authors discuss the gross and microscopic characteristics of the exudative processes found at autopsy in far advanced pulmonary tuberculosis. They studied especially the nonspecific processes, such as pulmonary edema, hepatization and splenization of the lungs. They conclude that the cause of death in many cases is frequently asphyxia due to the flooding of the lungs by this exudate, a conception which coincides with the fact that cyanosis, dyspnea and cardiac embarrassment are often seen clinically.

PERRY J. MELNICK.

ANOTHER CASE OF DEATH IN THE COURSE OF AN ASTHMATIC CRISIS. M. BRULÉ, P. HILLEMAND and J. DELARUE, Ann. d'anat. path. **12**:769, 1935.

After citing thirty-three cases described in the literature, the authors report an additional case with autopsy in a 45 year old woman who died during an attack of bronchial asthma. The disease was of only three years' duration and was precipitated by an electric shock from a current of 220 volts. The microscopic study of the lungs was of particular interest. Essentially, the changes consisted of extreme bronchorrhea, the smaller bronchi being much dilated and plugged by mucus, desquamated epithelium and eosinophil leukocytes. The bronchial musculature was thin. In addition there was marked local eosinophilia. The associated changes in the lung consisted chiefly of emphysema. The foregoing picture is interpreted as that of hyperactivity of vasomotor and secretory nerves rather than of bronchial spasm.

PERRY J. MELNICK.

DISSECTING BONE RESORPTION IN GENERALIZED OSTEODYSTROPHIA FIBROSA (RECKLINGHAUSEN'S DISEASE). K. THÜER, Virchows Arch. f. path. Anat. **295**:591, 1935.

Thüer presents a detailed histologic study of the bone changes in osteitis or osteodystrophia fibrosa as observed in a woman aged 38 years who had been ill for three years. The left lower parathyroid contained an adenoma with the dimensions of 2.7 by 3.2 cm. on the cut surface. There were no cysts or "brown tumors" of the bones. Such cysts, like the more advanced changes in the bones, are held to be late changes resulting from mechanical factors acting on the altered bones. The characteristic alteration, which occurs early and is illustrated in the case described, consists in the interlamellar resorption of both compact and spongy bone and in replacement of the resorbed bone and of the haversian canals by fibrous tissue. This process had been termed "interlamellar dissection" by Recklinghausen and "dissecting resorption" by Schmorl and Pick. This process is quite different from that which occurs in Paget's osteitis deformans, from which Recklinghausen's disease is to be distinguished. The latter is a disease sui generis of the osseous system due to parathyroid hyperactivity, although exogenous factors may play a part. In the case reported, anemia was not marked; the red marrow had undergone compensatory hyperplasia in response to the fibrosis of the marrow.

O. T. SCHULTZ.

SIGNIFICANCE OF LOESCHKE'S PERIVASCULAR SHEATHS. W. PFUHL, Virchows Arch. f. path. Anat. **295**:616, 1935.

By the use of vital stains Loeschke had recently detected sheaths or spaces about the capillaries, arterioles and venules. The cells bounding the sheaths, which Loeschke looked on as perivascular lymphatics, stain with the vital dyes. He ascribed to them great importance in normal resorption and in inflammation. Pfuhl, by intravital injections of trypan blue into guinea-pigs, confirmed Loeschke's observation of perivascular sheaths. He believes that in them occurs a fixation of bacteria and of toxic materials by the serum colloids.

O. T. SCHULTZ.

INFARCTS AND INFARCTION OF THE GALLBLADDER. G. MARK, Virchows Arch. f. path. Anat. **295**:645, 1935.

Mark reports two cases of localized multiple white infarcts of the gallbladder and two of more diffuse hemorrhagic infarction. In the first two cases the process was the result of arterial thrombosis in advanced arterial disease. In the third case the process was the result of thrombosis of numerous veins in a chronically inflamed gallbladder with endophlebitis. Arterial disease was a contributing factor. In the fourth case venous thrombosis was brought about by compression of the cystic vein and distention of the gallbladder by a carcinoma involving the duct. The clinical symptoms of the involvement of the gallbladder were not such as to lead to a suspicion of infarction.

O. T. SCHULTZ.

ALLERGIC VASCULAR REACTIONS IN LOCAL INFLAMMATORY PROCESSES. A. I. ABRIKOSSOFF, Virchows Arch. f. path. Anat. **295**:669, 1935.

Accepting the doctrine that the vascular reaction in a number of diseases is in response to the generalized action of some factor on a universally sensitized vascular system, Abrikossoff believes that hyperergic vascular changes may be mediated by a locally acting factor arising in a localized inflammatory process. In such a state the entire vascular system may be sensitized, but the allergic reaction occurs only in the locally inflamed field. As examples of such a possibility he mentions the vascular changes of the meninges in tuberculous and meningococcic meningitis and of the intestine in dysentery. In other instances the vessels are sensitized locally by an inflammatory process, which then evokes the hyperergic reaction in the vessels of the inflammatory field. In support of the latter thesis he describes the vascular changes in cases of chronic mastitis, chronic pyelitis, appendicitis and recurrent valvular endocarditis. He believes that this process may be an important factor in establishing the chronicity of an inflammatory process and in leading to granuloma.

O. T. SCHULTZ.

A WANDERING CELL OF SMOOTH MUSCLE ORIGIN. Y. HAMAZAKI, Virchows Arch. f. path. Anat. **295**:703, 1935.

By means of special fixing and staining methods, which are described, Hamazaki claims to have discovered a new type of wandering cell that has hitherto gone unrecognized. The cell is short and fusiform and may become oval or rounded. The cytoplasm contains granules of three types: acid-fast, alkali-fast, and iodine-fast with an affinity for mercury. Because of their granulation the cells are highly refractile; hence they have been termed *Glanzzellen* or "shiny cells." They are fairly numerous in normal smooth muscle and adjacent connective tissue. They have been found only in smooth muscle of man and the monkey. Their origin has been traced to smooth muscle fibers. In the past they have probably been confused with histiocytes, fibrocytes and tissue mast cells. Familiarity with their characteristics in special stains permits their recognition in the usual hematoxylin-eosin preparation. Their function is as yet unknown; their number is increased in chronic inflammation of smooth muscle.

O. T. SCHULTZ.

PATHOLOGY OF PULMONARY EPITUBERCULOSIS. R. RÖSSLE, Virchows Arch. f. path. Anat. **296**:1, 1935.

Rössle would limit the term "epituberculosis" to the form of pulmonary tuberculosis of children in which a relatively large and deep roentgen shadow clears with apparent restoration of the pulmonary tissue to normal; the condition runs a benign course and ends in recovery. An anatomic explanation of the process is wanting, because few of the patients followed during life come to autopsy. The clinical explanation based on roentgen findings is that the process is perifocal inflammatory infiltration, which may be tuberculous or nonspecific, in the latter case often being considered tuberculotoxic. Rössle objects to this interpretation because the shadow may be eccentric to the tuberculous focus rather than perifocal, or it may even be in a lobe other than that which has the tuberculous focus. He describes eight cases that give a clue as to what happens and explains some of the less typical outcomes. The roentgen shadow is due to obstructive compression of a large bronchus by a hilar node in the area of the primary complex, with atelectasis of the lung of the occluded bronchus. Smaller bronchi may be occluded by an intrapulmonary node. Clearing of the shadow is due to subsequent aeration of the collapsed lung. In cases presenting a less typical course bronchial occlusion and atelectasis were caused by tuberculous bronchitis following invasion of the bronchus from a tuberculous focus. In such instances the tuberculous process may be progressive. Another atypical variation may be due to incomplete bronchial obstruction by nonspecific desquamative catarrhal pneumonia.

O. T. SCHULTZ.

GLANDULAR HYPERPLASIA OF THE MUCOSA OF THE CARDIA OF THE STOMACH. H. HAMPERL, Virchows Arch. f. path. Anat. **296**:39, 1935.

Systematic gross and microscopic examination of the cardia of the stomach in a series of cases covering all age groups revealed the frequent occurrence of diffuse or nodular hyperplasia of the mucous glands of the mucosa. Observed in the second decade of life, the process became progressively more frequent from the fortieth year on. All the factors underlying the process are not known, but aging of the tissues is held to be the most important one. Replacement of esophageal by gastric mucosa, described in detail in one case, is interpreted as the result of the healing of peptic esophagitis.

O. T. SCHULTZ.

HISTOLOGY OF THE GASTRIC MUCOSA. H. HAMPERL, Virchows Arch. f. path. Anat. **296**:82, 1935.

As a by-product of his systematic examination of the gastric mucosa Hamperl describes a number of histologic minutiae that may be of some interest but are of little importance. He notes: mucigenous granules in the pyloric cells; occasional beaker cells filled with mucus among the surface epithelial cells; frequent fat droplets in the gland cells; cells with homogeneous eosinophilic protoplasm in the mucous glands of the cardia in two cases, similar to the onkocytes of the salivary glands, which Hamperl has held to be the result of senile change in mucous cells; vacuolar degeneration of mucous cells, and in one instance the presence of "protozoon-like" cells similar to those that have been described in other human tissues and which he believes to be the result of nucleolar hypertrophy and degeneration.

O. T. SCHULTZ.

Microbiology and Parasitology

EXPERIMENTAL MENINGOCOCCIC INFECTION IN THE MOUSE. C. P. MILLER and R. CASTLES, J. Infect. Dis. **58**:263, 1936.

It was possible to initiate fatal infections regularly in mice by intraperitoneal inoculation of very few meningococci suspended in mucin prepared from hog's gastric mucosa. With the authors' most virulent strains, approximately ten organisms sufficed.

Multiplication of meningococci inoculated into the peritoneal cavity in mucin suspension did not occur during the first few hours, but thereafter it proceeded rapidly. The blood stream was always invaded at some time during the course of infection, within the first hour if the infecting dose was large. Little phagocytosis was seen in peritoneal exudates of animals infected with virulent strains, but considerable phagocytic activity was seen in those of animals inoculated with less virulent organisms. The ability of mucin to facilitate intraperitoneal infection with meningococci persisted for several hours; thereafter the resistance increased. Sterile mucin in the peritoneal cavity also promoted infection by the intravenous route. Mucin in the subcutaneous tissues failed to do so. No evidence was found that mucin raises the virulence of meningococci. The apparent enhancement of their invasiveness seems to be due to local interference with the defense mechanism of the host.

Monovalent rabbit antimeningococcic serums were found to protect mice effectively against inoculation with numbers of meningococci many times the minimum fatal dose. Below a maximum 10,000,000 M.F.D. these multiples were roughly proportional to the quantity of serum administered. Among the serums tested, those belonging to types I to III protected (within the limits of their potency) against all the strains of this type. Similarly the three type II serums examined were effective against the three strains of this type. Serums of one type protected poorly or not at all against strains belonging to another. In short, the monovalent serums examined were type-specific in their protective action. The protection afforded by a large dose of serum persisted in quite high degree for

about two weeks. Immune serum averted a fatal outcome even when administered after the infection was quite well developed. Four of six polyvalent therapeutic serums tested were as effective as the authors' most potent rabbit serum, and another nearly so. The mouse protection test is suggested as a means of standardizing therapeutic serums.

FROM THE AUTHORS' SUMMARY.

A DIFFERENTIAL STUDY OF FORTY STRAINS OF BRUCELLA ISOLATED IN MINNESOTA. P. KABLER and M. MACLANAHAN, J. Infect. Dis. **58**:293, 1936.

The forty strains have been classified as follows: 25, Brucella suis; 13, Brucella abortus, and 2, doubtful. Of the latter, one appeared to be Brucella suis and one Brucella melitensis. The agglutinin absorption method is of little value in the differentiation of such strains in Minnesota. The oxygen tension originally required together with the characteristics of the growth gave on dye plates fairly reliable differentiation. The strains isolated in Minnesota from human beings with undulant fever indicated that Br. suis is the etiologic agent about twice as often as Br. abortus.

FROM THE AUTHORS' SUMMARY.

STAPHYLOCOCCIC FOOD POISONING. H. J. SHAUGHNESSY and T. C. GRUBB, J. Infect. Dis. **58**:318, 1936.

The investigation of a small epidemic of food poisoning involving some twenty-five persons is described in which there was little doubt that the consumption of raw milk from cows with staphylococcic mastitis was the cause of the poisoning. The most convincing circumstantial evidence thus far recorded that ice cream may also serve as a vehicle for enterotoxic substances produced by staphylococci is indicated by this investigation. A hemolytic staphylococcus of the albus variety was isolated from the incriminated milk which, under suitable laboratory cultivation, produced a toxic substance capable of causing vomiting in monkeys and man. It appears probable, therefore, that the cause of the food poisoning was the consumption of milk or ice cream containing a gastro-intestinal irritant elaborated by one and perhaps other strains of staphylococci isolated from the milk. It seems possible that if the recently described technical methods for determining the ability of micro-organisms to produce enterotoxin are utilized on streptococci and staphylococci from infected udders, milk from cows with mastitis may not appear so innocuous as formerly it did.

FROM THE AUTHORS' SUMMARY.

THE RECOVERABILITY OF MYCOBACTERIUM TUBERCULOSIS AVIUM FROM EXPERIMENTALLY INFECTED GUINEA-PIGS. W. H. FELDMAN, J. Infect. Dis. **59**:1, 1936.

The recoverability of Mycobacterium tuberculosis avium from experimentally infected guinea-pigs was demonstrated. Thirty-four guinea-pigs were inoculated subcutaneously with suspensions of virulent organisms. Necropsy was made from one to seventy days subsequently, and the spleens were emulsified and cultured. The avian tubercle bacillus was obtained from eight of the twenty guinea-pigs examined at necropsy up to and including twenty-one days after receiving the infective inoculum. Of the fourteen animals examined at necropsy from twenty-eight to seventy days after the infection was introduced, thirteen yielded the specific micro-organism. Macroscopic lesions of a tuberculous character were present in only one of the forty-three animals examined. These results show that the organism of avian tuberculosis may be recovered from the spleens of previously inoculated guinea-pigs, although gross lesions of tuberculosis are usually absent. This suggests the advisability of culturing the spleens of guinea-pigs as a routine in the study of clinical material in which the presence of the avian tubercle bacillus is suspected.

FROM THE AUTHOR'S SUMMARY.

ACUTE INFECTIOUS MONONUCLEOSIS WITH UNIDENTIFIED STRUCTURES IN SUPRAVITAL PREPARATIONS OF LYMPH NODES. L. A. ERF, J. Mt. Sinai Hosp. **3**: 113, 1936.

Scrapings of lymph nodes from three patients with the clinical and hematologic findings of infectious mononucleosis, when examined with supravital methods, revealed cysts about the size of red cells, filled with a clear yellow fluid containing from ten to fifteen comma-shaped or irregular actively motile brownish black inclusions. Cultures from the lymph nodes and injections of emulsions into guinea-pigs, rabbits and mice revealed nothing. The first patient had bronchopneumonia in the early stages, which followed a rather atypical course. Her blood showed in supravital and dark field preparation structures resembling the inclusions in the cysts of the lymph nodes. The lymph nodes of a monkey that was inoculated intravenously with that blood showed two weeks later cysts similar to those revealed in the human preparations. In only one of the three cases was there positive evidence for the presence of heterophilic antibodies. In the lymph nodes of five other patients with typical infectious mononucleosis, the cysts with inclusions could not be found. Erf bases the diagnosis of infectious mononucleosis on clinical and hematologic data. In only 40 per cent of his patients with this condition was a test for heterophilic antibodies positive.

I. DAVIDSOHN.

BRAIN REACTION IN GUINEA-PIGS INFECTED WITH ENDEMIC TYPHUS, EPIDEMIC (EUROPEAN) TYPHUS AND ROCKY MOUNTAIN SPOTTED FEVER, EASTERN AND WESTERN TYPES. R. D. LILLIE and R. E. DYER, Pub. Health Rep. **51**:1293, 1936.

The character of the individual focal brain lesion in the guinea-pig is not notably different with strains of endemic and epidemic typhus and with eastern and western strains of Rocky Mountain spotted fever. The proportion of local lesions in the midbrain, pons, medulla and cerebellum in Rocky Mountain spotted fever, especially in that produced with the eastern strains, is notably higher than that found in either of the typhus fevers. Proliferative types make up a higher proportion of the vascular lesions in spotted fever than in typhus. The length of the period of incubation has no discernible influence on the intensity of the brain reaction in endemic typhus. All the typhus and spotted fever strains studied show a relatively low intensity of brain reaction in the first week, then a rapid rise in number of lesions for about two days, a "plateau" of maximum reaction lasting from three to four days in the second week and a late period of subsidence. In typhus, perivascular lymphocyte infiltration is relatively more frequent in the "plateau" period of maximum reaction; "nodes" and proliferative vascular lesions, earlier and later. The frequency of recognizable brain reactions in endemic typhus and the spotted fevers is also greatest in the "plateau" period. The presence of scrotal and testicular reaction in endemic typhus does not decrease the intensity of the brain reaction, but rather the reverse. Clinically mild or complicated endemic typhus shows a less intense brain reaction than uncomplicated typhus with definite scrotal reaction. The presence of cultivable micro-organisms in the cardiac blood at autopsy is associated with lowered intensity of the brain reaction. Testicular washings in endemic typhus as inocula give greater frequency and intensity of brain reactions during the period from the ninth to the thirteenth day than does blood.

FROM THE AUTHORS' SUMMARY.

UNRECOGNIZED POSTOPERATIVE INFECTION. A. S. W. TOUROFF, Surg., Gynec. & Obst. **62**:941, 1936.

The literature contains many reports of a postcholecystectomy syndrome of unexplained rapid rise in temperature, acceleration of the pulse and respiration, shock and vasomotor collapse, ending in early death. When it has been possible to eliminate clinically all postoperative complications, such a syndrome has been attributed commonly to what has been termed "liver shock." Most persons who have

died of this condition have not been subjected to adequate postmortem examination in order to corroborate the diagnosis. In four patients with so-called hepatic shock coming to autopsy Touroff found the cause of death to be unrecognized fulminating intraperitoneal or pulmonary infection rather than hepatic damage.

FROM THE AUTHOR'S SUMMARY. (WARREN C. HUNTER.)

THE EFFECT OF THE VIRUS OF LOUPING ILL ON THE DEVELOPING EGG. F. M. BURNET, Brit. J. Exper. Path. **17**:294, 1936.

The virus of louping ill may be propagated in the developing egg of the hen, in which it produces both local lesions of the chorio-allantoic membrane and general effects on the embryo. The number of focal lesions can be used as a sensitive but rather inaccurate indicator of the amount of virus present. Serum neutralization tests can be carried out with egg membrane as the indicator, the results agreeing fairly closely with those obtained by intracerebral inoculation in mice. The virus is constantly present in the circulating blood, is in part at least attached to the blood cells, and is liberated from this attachment by the action of distilled water. The lesions observed in the embryo are such as might be accounted for if the primary effect of this virus is to produce hemolytic anemia with or without primary damage to the hepatic cells. The almost exclusive viscerotropism of the virus in this situation is discussed.

FROM THE AUTHOR'S SUMMARY.

THE TYPHUS GROUP OF DISEASES IN MALAYA. R. LEWTHWAITE, E. P. HODGKIN and S. R. SAVOOR, Brit. J. Exper. Path. **17**:309, 1936.

Transmission of the virus of urban typhus under experimental conditions from rat to rat by the rat flea (Xenopsylla cheopis) by feeding has been effected. Collateral attempts to transmit the virus of rural typhus by precisely the same procedure failed. Transmission of the virus of urban typhus was also achieved by inoculation of feces or of crushed tissue of infected fleas into the scarified skin of guinea-pigs. Multiplication of the virus of urban typhus occurs within the rat flea. Infection with the virus of urban typhus is not hereditary in the rat flea. Attempts to transmit the virus of urban or rural typhus by two species of ticks failed. In the case of rural typhus a lessened mortality in the experimental guinea-pigs following test inoculation with passage virus makes it, however, difficult to exclude ticks entirely as a minor factor in the epidemiology of rural typhus.

FROM THE AUTHORS' SUMMARY.

BACTERIOPHAGE SPECIFIC FOR THE V FORM OF BACILLUS TYPHOSUS. J. CRAIGIE and K. F. BRANDON, J. Path. & Bact. **43**:233, 1936.

Bacteriophage specific for the V form of Bacillus typhosus may be present in cultures of this organism derived from the stools of patients and carriers. Sensitivity to V bacteriophage and capacity to absorb it are intimately related to the presence of V agglutinogen; the W form of B. typhosus and other species of Salmonella which do not elaborate this antigen are resistant. Exposure of the V form of B. typhosus to V phage results in its conversion to the phage-resistant W form, with loss of V agglutinogen and capacity to absorb the phage. V phage is of value in the identification of the V form of B. typhosus, in the detection of W degradation and in the maintenance of pure V cultures.

FROM THE AUTHORS' SUMMARY.

V AND W FORMS OF BACILLUS TYPHOSUS. J. CRAIGIE and K. F. BRANDON, J. Path. & Bact. **43**:249, 1936.

The V form of Bacillus typhosus is present in a very high percentage of typhoid carriers and of patients. Occasionally, cultures of B. typhosus from stool specimens are lysogenic or lytic, yielding V phage which converts the V form to the W form.

In the absence of demonstrable V phage, strains of B. typhosus vary one from another in their tendency to degrade to the W form. Reversion of the W form to the V form on laboratory mediums is probably very rare. It cannot be inferred that a human infection is due solely to the W form of B. typhosus unless freshly isolated cultures are examined and the presence of V phage in the specimen of origin is excluded. Since a very high percentage of freshly isolated cultures of B. typhosus are practically pure cultures of the V form, V phage is of definite diagnostic value. The V form in young broth cultures exhibits complete O resistance, but this property is partly lost by the majority of strains on incubation for eighteen hours.

FROM THE AUTHORS' SUMMARY.

CULTIVATION OF THE VIRUS OF ECTROMELIA ON THE CHORIO-ALLANTOIC MEMBRANE OF HEN'S EGGS. E. PASCHEN, Zentralbl. f. Bakt. (Abt. 1) **135**:445, 1936.

The virus of infectious ectromelia was cultivated successfully on the chorio-allantoic membrane of hen's eggs for eighteen passages, during which time the virus of the cultures could be implanted in the skin or corneas of rabbits as well as in the feet of guinea-pigs. Typical inclusions could be demonstrated in the lesions. Primary injections of the original mouse virus into the skin of rabbits and guinea-pigs yielded negative results. Paschen concludes, therefore, that cultivation of the virus on the chorio-allantoic membrane causes a change in the biologic character of the virus.

PAUL R. CANNON.

THE GENESIS OF DIPHTHERIA WITH ESPECIAL REGARD TO THE VIRULENCE OF TYPES OF DIPHTHERIA BACILLI. M. GUNDEL and NIYAZI ERZIN, Zentralbl. f. Bakt. (Abt. 1) **136**:24, 1936.

The authors investigated the invasive and toxicogenic powers of ten strains of diphtheria bacilli of the types gravis, intermedius and mitis when injected subcutaneously into guinea-pigs. The gravis type exhibited high toxicity and marked invasive potentiality, as shown by its rapid dissemination to many organs. The intermedius type was somewhat less toxic, but in fatal infections it was usually cultured from various internal organs. The mitis type led to delayed deaths and was usually absent from the viscera. The authors were impressed by the frequent recovery of diphtheria bacilli from the tonsils after subcutaneous injection (in 32 of 140 guinea-pigs tested); they discuss the relationship of this finding to the possible rôle of the tonsils in the dissemination of diphtheria bacilli through the lymphatic vessels in anginal diphtheria.

PAUL R. CANNON.

INTESTINAL CHANGES IN MICE AFTER VARIOUS MODES OF INFECTION WITH BACILLUS ENTERITIDIS BRESLAU. A. WALDMANN and E. ROSTOWA, Zentralbl. f. Bakt. (Abt. 1) **136**:49, 1936.

White mice were infected enterally with the Breslau type of Bacillus enteritidis, either by a drop of broth culture orally or by mixing the micro-organisms with bread. Death occurred within from six to twelve days regardless of the size of the infecting dose or the mode of infection. Pathologic examination of Peyer's patches, mesenteric lymph nodes, liver and spleen showed a marked difference in relation to the mode of infection. Peyer's patches and the mesenteric lymph nodes were distinctly hyperplastic in mice infected by food-borne bacilli, whereas they were almost normal in mice infected orally with broth cultures. The liver and spleen were abnormal in all three groups.

The authors conclude that oral ingestion of a liquid culture probably leads to generalization of the bacteria through the lymphatic structures of the throat, and that the pathologic effects simulate those resulting from parenteral infection. In infection by way of the food, however, a "primary complex" results (Peyer's patches and adjacent mesenteric lymph nodes), followed by generalization.

PAUL R. CANNON.

COLONIZATION OF COLON BACILLI IN THE INTESTINES OF MICE. T. LINK, Zentralbl. f. Bakt. (Abt. 1) **136**:63, 1936.

Link attempted to implant a strain of Bacillus coli (strain 88 of Gildemeister and Herzberg) in mice by feeding them organisms and looking for the bacteriophage for dysentery bacilli which is formed by this micro-organism. Mice were used which contained in their feces no bacteriophage for the dysentery bacilli employed in the tests. Colonization was secured up to twelve days in only 4 of 96 cases. No bacteriophage was demonstrated in the blood of these animals. Strain 88, after several days in the intestines of mice, still retained its ability to liberate bacteriophage.

PAUL R. CANNON.

STUDIES ON STAPHYLOCOCCI. J. FORSSMAN and A. FLAUM, Acta path. et microbiol. Scandinav. **13**:263 and 453, 1936.

Despite specific antibodies in the blood, staphylococci thrived in the vertebral marrow of the rabbit and were destroyed slowly in other tissues. Agglutinins and opsonins were obtained by injecting formaldehydized staphylococci, and antilysins by injecting formaldehydized filtrates of broth cultures of staphylococci. The immunity curve following injections of formaldehydized staphylococci and that following injections of sterile bacterial cultures were closely parallel. In from two to three weeks after the last injection, immunity increased, only to subside to a minimum, then rose rapidly to complete protection in from two to three months. The degree of immunity was never as high as in experiments with streptococci or pneumococci. The serum of the immunized rabbits contained antidermonecrotic antibodies, which neutralize staphylococcic toxin and thus prevent necrosis of the skin in any area into which a mixture of serum and toxin is injected. The serum of these immunized rabbits afforded no protection to rabbits but was effective in other animals. It was also observed that the serum from immunized sheep protected rabbits against the micro-organisms and contained both antilysins and antidermonecrotic substances. Such properties probably play an important rôle in resistance to staphylococcic infections. The neutralization of lysins may not be a reliable measure of the therapeutic efficacy of antistaphylococcic serums, since lysins were obtained which dissolved sheep corpuscles, though not rabbit corpuscles, and hemolysins were found which were neither capable of causing skin necrosis nor lethal.

FREDERICK STENN.

Immunology

HETEROPHIL HEMAGGLUTININ IN RABBITS WITH "SERUM SICKNESS." H. A. KEMP and B. O. BAKER, Am. J. Clin. Path. **6**:557, 1936.

A development of heterophilic agglutinins for sheep red cells was found in rabbits in which serum reactions were produced by injection of large quantities of horse serum (6 cc. per kilogram of body weight). The titer was proportionate to the severity of the serum reaction.

I. DAVIDSOHN.

ABSORPTION OF HETEROPHIL HEMAGGLUTININ BY BEEF CORPUSCLES. H. A. KEMP and B. O. BAKER, Am. J. Clin. Path. **6**:560, 1936.

In four cases of infectious mononucleosis, beef erythrocytes removed agglutinins for sheep erythrocytes as had been reported by Bailey and Raffel. The same antigen failed to act similarly on the antisheep agglutinins in the blood of patients with rashes caused by drugs or with serum disease and in the blood of rabbits with agglutinin elevated following injections of horse serum.

I. DAVIDSOHN.

STAPHYLOCOCCIC IMMUNITY. J. S. KITCHING and L. N. FARRELL, Am. J. Hyg. **24**:268, 1936.

Active immunization of rabbits and mice with staphylococcus toxoid produced an increase in resistance against the lethal effect of staphylococci and staphylotoxin introduced parenterally and also against the dermonecrotic effect of staphylotoxin introduced intradermally in rabbits. In general, the protection against these two effects depended on the amount of circulating antitoxin as determined by serum titrations, the "standard unit" being used as a basis for comparison. In rabbits the titer of circulating antitoxin fell off approximately ten days after the last of a course of injections of toxoid. The drop was at first sharp, to approximately half, then gradual. The titer could be raised approximately to its former maximum by one further injection of toxoid. Treatment of rabbits and mice with formaldehydized staphylococcus vaccine, prepared and used under the conditions described, produced little or no circulating antitoxin and no increase in resistance against the lethal effect of staphylococci and staphylotoxin introduced parenterally or against the dermonecrotic effect of staphylotoxin in rabbits. The serum obtained on injecting formaldehydized staphylococcus vaccine into rabbits, in the quantity used, did not confer passive immunity against the lethal effect of staphylococci in rabbits and mice. Staphylococcus antitoxin was found definitely to confer passive immunity against the lethal effect of living staphylococci and staphylotoxin introduced parenterally into rabbits and mice. The immunity was in direct proportion to the number of units of antitoxin given. Antitoxin given intravenously before the injection of toxin was found to have a modifying effect on the toxin damage to tissues and, under the conditions of the experiment, definitely to prevent the lethal effect of the toxin or of the micro-organisms. Delay in administration of antitoxin, particularly when the subcutaneous route was used, distinctly lessened its value.

FROM THE AUTHORS' SUMMARY.

NEUTRALIZING ANTIBODIES FOR THE VIRUS OF HUMAN INFLUENZA IN THE SERUM OF PERSONS WITH HISTORIES OF INFLUENZA. H. W. BROWN, Am. J. Hyg. **24**:361, 1936.

Neutralization tests, using mice, were made with influenza virus (Puerto Rico 8 strain) and the serum of persons with various histories of attacks of influenza, with the following results: Neutralizing antibodies were present in the serum of 74 per cent of the adults who had had influenza during the 1918-1919 pandemic but who had not had the disease since that time. Among those tested were persons recently arrived from Albania, Rumania, Argentina, Esthonia and Canada. Adults who had passed through the 1918-1919 pandemic and subsequent seventeen years without an attack of influenza possessed potent antibodies. The incidence of antibodies to the Puerto Rico 8 strain of influenza virus in children from 3 to 12 years of age was approximately the same as the incidence in the adults tested. Such antibodies were encountered infrequently in children under 3 years of age. Neutralizing antibodies to this strain in the serum of persons convalescent from an illness diagnosed as sporadic influenza were no more potent than the antibodies present in their serum previous to the disease. Attempts to recover a filtrable virus pathogenic for ferrets from three persons whose illness had been diagnosed as influenza—a small institutional epidemic—all failed. Neutralization tests in mice with the serum obtained from these patients during their illness and also after their convalescence indicated that no appreciable change had occurred in the content of antibodies to the Puerto Rico 8 strain of influenza virus.

FROM THE AUTHOR'S SUMMARY.

REACTION FOLLOWING INTRA-GROUP BLOOD TRANSFUSION. C. G. CULBERSTON and A. W. RATCLIFFE, Am. J. M. Sc. **192**:471, 1936.

A maternity patient of group 0 was given 500 cc. of her husband's blood, also of group 0. At the end of the transfusion she had a chill, and her temperature rose to 105 F. Hemoglobinuria and oliguria followed for a few days, and the

total nonprotein nitrogen in the blood gradually rose to 235 mg. per hundred cubic centimeters. With symptomatic treatment the patient gradually improved but did not fully recover for seven weeks. Examination of her serum by the centrifuge technic showed that it agglutinated twenty-three of twenty-four group 0 bloods. The serum was also sent to Dr. K. Landsteiner, who found that it agglutinated twenty of twenty-three group 0 bloods which he tested. In a second case, a similar irregular agglutinin which acted on three group 0 bloods tested was detected by the cross-match. The mother of the recipient was found to have compatible blood, and 550 cc. was transfused without mishap. These cases demonstrate the importance of performing a cross-match before transfusion, even when the donor and the recipient belong to the same blood group.

A. S. WIENER.

NEPHROSIS WITH UREMIA FOLLOWING TRANSFUSION OF INCOMPATIBLE BLOOD. W. GOLDRING and I. GRAEF, Arch. Int. Med. **58**:825, 1936.

Observations are reported on seven patients with a severe hemolytic reaction following transfusion of incompatible blood; four recovered, and three died. The reaction was characterized by a sudden onset of oliguria (in instances of severe involvement, anuria) and hemoglobinuria and gradual development of renal insufficiency and uremia. Mistakes in grouping accounted for the reaction in three patients; in two, failure to recheck the grouping after the transfusion left doubt as to the classification; in two, regrouping showed the bloods of the donor and recipient to be of the same group. In the latter two patients the reaction was unpredictable and therefore, in the present state of knowledge of blood groups and methods for their identification, must be considered unavoidable. Pathologic observations in two of the three fatal cases revealed a necrotizing process affecting the uriniferous tubules which was like that seen in mercurial nephrosis. Distinctive pigment casts containing hemoglobin or its derivatives were conspicuous, and interstitial edema increased the size of the kidneys. Central focal necrosis was observed in the liver of one patient.

FROM THE AUTHORS' SUMMARY.

EFFECT OF SALTS ON THE PRECIPITIN REACTION. M. HEIDELBERGER, F. E. KENDALL and T. TEORELL, J. Exper. Med. **63**:819, 1936.

A quantitative study has been made of the effect on the precipitin reaction between the specific polysaccharide of the type III pneumococcus and the homologous antibody of salt concentrations ranging from 0.1 to 1.79 molar, including the effect of ions of higher valence. Within these limits, the observed decrease in precipitated antibody with increase in salt concentration appears to be due to decrease in the antibody combined with the S III, rather than to increase in solubility of the S III-antibody compounds. The egg albumin-antibody reaction is far less sensitive to changes in salt concentration than is the S III-antibody reaction.

FROM THE AUTHORS' SUMMARY.

PERSISTENCE OF THE VIRUS OF LYMPHOCYTIC CHORIOMENINGITIS IN IMMUNE ANIMALS AND ITS RELATION TO IMMUNITY. E. TRAUB, J. Exper. Med. **63**:847, 1936.

In some apparently healthy mice the virus of lymphocytic choriomeningitis persisted in the blood, urine and nasal secretions for a considerable period after recovery, while in other mice it soon became undemonstrable. It is possible that this persistence of the virus was due to lesions in the lungs, liver and kidneys. Immunity to lymphocytic choriomeningitis in mice does not seem to depend on the presence of virus in the blood and the organs tested. No antivirus was detected in serums from several solidly immune mice, a fact which suggests that circulating antivirus plays no important part in their immunity. Leukocytes also seem to be

nonessential in this immunity, which probably is closely linked with the tissues. The urine of guinea-pigs which had recovered from severe attacks of lymphocytic choriomeningitis contained virus for a few weeks after recovery, while that from guinea-pigs which had had mild attacks contained no virus. The virus was never demonstrated in the blood of immune guinea-pigs. Antivirus was readily detected in it.

FROM THE AUTHOR'S SUMMARY.

PROTECTIVE ACTION OF NASALLY INSTILLED IMMUNE SERUM AGAINST INFECTION WITH CERTAIN NEUROTROPIC VIRUSES INTRODUCED BY WAY OF THE NOSE. A. B. SABIN, J. Exper. Med. **63**:863, 1936.

Immune serum instilled intranasally into guinea-pigs protected them from infection with lethal amounts of the virus of pseudorabies introduced by the nasal route. Protection was similarly obtained in mice against the virus of equine encephalomyelitis (eastern strain). The protective effect began at the time of instillation, was still evident five hours later and usually had disappeared by the end of twenty-four hours. Attempts to prolong the local effectiveness of immune serum by several devices were unsuccessful. The action appears to be local in the nose in view of the fact that the administration of even larger amounts of the immune serum intramuscularly failed to protect guinea-pigs against infection with the virus of pseudo-rabies introduced by the nasal route.

FROM THE AUTHOR'S SUMMARY.

ANTILEUKOCYTIC SERUM. W. B. CHEW, D. J. STEPHENS and J. S. LAWRENCE, J. Immunol. **30**:301, 1936.

Antileukocytic serum was produced by intravenous injections of leukocytes of guinea-pigs into rabbits. The hemolytic antibodies of this serum were removed by absorption with red blood cells of guinea-pigs. Following intravenous injections of the serum into guinea-pigs marked depression of the number and for a time even complete disappearance of neutrophilic leukocytes took place. There was also a slight decrease in the number of the lymphocytes but no essential change in the numbers of the other constituents of the blood. Intraperitoneal injections of the serum had similar effects, but it took a considerably longer time for these effects to appear. Repeated injections produced tolerance to the leukotoxic serum; to produce the initial effect the dose of the serum had to be gradually increased. Histologic sections of different tissues showed not an increase in the number of the neutrophilic leukocytes, but a steady decrease, reaching its lowest point twenty-four hours after the injection of the serum. After repeated injections there was marked hyperplasia of the neutrophils. No evidence of damage to any body cells was noted. Subcutaneous injections of staphylococci and intraperitoneal injections of mixtures of acacia failed to produce a local increase in the number of leukocytes; such an increase was noted in control animals.

I. DAVIDSOHN.

VARIATION IN THE SUSCEPTIBILITY OF GUINEA-PIGS TO REVERSED PASSIVE ANAPHYLAXIS. H. ZINSSER and J. F. ENDERS, J. Immunol. **30**:327, 1936.

Sixteen guinea-pigs from among twenty-two of one stock reacted with typical anaphylactic symptoms and lesions, observed at autopsy, to injections of horse serum followed within from one and one-half to ten minutes by a rabbit antihorse serum of a sufficiently high titer. The same phenomenon occurred when the reagents were injected in the reverse order. Only one guinea-pig of twenty-four from other stocks reacted similarly, while the other animals did not respond. Zinsser and Enders suggest that the susceptibility may be hereditary.

I. DAVIDSOHN.

THE NONIDENTITY OF THE ANTIGENIC AND ANTITOXIC GROUPS IN DIPHTHERIA ANTITOXIN. H. EAGLE, J. Immunol. **30**:339, 1936.

Eagle confirmed the observation of Eisler that diphtheria antitoxin even after combination with toxin could be precipitated by a rabbit antiserum vs. horse serum and that of Smith and Marrack that diphtheria antitoxin precipitated by a rabbit antiserum could still bind toxin. He showed in addition that saturation with a large excess of toxin in one case and with a large excess of antiserum in the other did not affect the reactions. Eagle concludes that the molecule of the diphtheria antitoxin has apparently different combining sites for toxin and for precipitin.

I. DAVIDSOHN.

THE NATURE OF A VIRUCIDAL SUBSTANCE IN "NORMAL" HUMAN SERUM. P. S. STRONG, J. Immunol. **30**:403, 1936.

Virucidal properties against the presumably herpetic "W" virus were found in about 70 per cent of human serums. These properties did not depend on the presence of complement; they were not affected by ammonium hydroxide, resisted heating up to 64 C. and were destroyed completely only by a temperature of 80 C. Absorption with bacteria and other particulate matter did not remove the virucidal factors from the serum. Neutral mixtures of virus and antibody could be rendered infective by dilution within two hours, indicating that no permanent union took place within that time. After six hours, dilution did not restore the infectivity, but this result was due to deterioration. Injection of a virucidal serum into rabbits proved the antigenicity of the virucidal substance by the production of a neutralizing antivirucidal substance. Various considerations suggest, according to Strong, that the virucidal substance is not of the nature of an antibody in the strict immunologic sense.

I. DAVIDSOHN.

ANTIGENIC CHARACTERISTICS OF RELATED ORGANISMS AFTER CULTIVATION ON SYNTHETIC MEDIUM. P. J. BEARD and J. E. SNOW, J. Infect. Dis. **59**:40, 1936.

The data presented are yet too limited to permit any final conclusions, but, on the basis of the experiments carried on to date, it is suggested that true biologic relationships may be obscured as an effect of environmental conditions or, conversely, that characters regarded as biologically inherent may arise as an effect of environment.

The experiments are being carried on, and further efforts toward simplification of mediums are in progress.

FROM THE AUTHORS' SUMMARY.

RELATIONS BETWEEN CERTAIN HETEROPHIL ANTIBODIES AND ANTIGENS. C. A. STUART and others, J. Infect. Dis. **59**:65, 1936.

The antibodies for sheep erythrocytes in infectious mononucleosis are distinguished from normal human antibodies for sheep cells by being adsorbed by beef erythrocytes and not by guinea-pig kidney.

The agglutinins for sheep erythrocytes in serum sickness are distinguishable from normal sheep agglutinins, but apparently this is not true of the lysins in the same disease.

Sheep cell agglutinins and lysins arising in rabbits given injections of human group A cells are not adsorbed by the erythrocytes which specifically remove any of the other antibodies under discussion.

The apparent coexistence of heterophil antigen and antibody in human blood of group A may be accounted for by a multiplicity of heterophil antibodies, all of which possess the cardinal character of such antibodies, namely, ability to react with sheep erythrocytes, but differ in that they fail to react with certain other heterophil antigens and may react with certain nonheterophil cells.

FROM THE AUTHORS' SUMMARY.

H AND O AGGLUTININS AND COMPLEMENT-FIXING BODIES IN PERSONS INOCULATED WITH TYPHOID ENDOTOXOID VACCINE. E. GRASSET and W. LEWIN, Brit. J. Exper. Path. **17**:179, 1936.

The serum of persons inoculated with typhoid endotoxoid vaccine produced by the South African Institute for Medical Research showed the presence of H and O agglutinins—in the large majority of cases, in high titer. A concentrated antigen produced a higher O agglutinin response than this regular product. The titer for H agglutinins shortly after inoculation is much higher than that for O agglutinins, but the titer of the latter remains more constant, while the titer for H agglutinins falls rapidly. At some stage during inoculation complement-fixing bodies were present in approximately 32 per cent of persons inoculated with endotoxoid vaccine of a concentration issued for human use. A more concentrated antigen, given seven persons, produced complement fixation in all cases. Of serums from thirty-three persons examined seven months after the last injection, four, or 12 per cent, gave complement fixation. An O agglutination test performed with a serum dilution of 1:200 will not aid in diagnosis in the case of a person with a febrile illness who has been recently inoculated with typhoid endotoxoid vaccine. Inoculation of a population with such a vaccine will limit the use of H and O agglutination tests and the typhoid complement fixation test for the detection of the carrier state.

FROM THE AUTHORS' SUMMARY.

THE POLYSACCHARIDE COMPLEX AND VARIANTS OF VIBRIO CHOLERAE. P. B. WHITE, Brit. J. Exper. Path. **17**:229, 1936.

The smooth cholera vibrio possesses four serologically active polysaccharide or nonprotein carbohydrate-containing constituents.

FROM THE AUTHOR'S SUMMARY.

THE IMMUNIZING PROPERTIES OF UNDILUTED AND DILUTED DIPHTHERIA FORMOL-TOXOID. W. A. TIMMERMAN and A. C. BRANDWIJK, Brit. J. Exper. Path. **17**:252, 1936.

The immunizing power of a fixed quantity of a certain diphtheria toxin digested with dilute solution of formaldehyde is dependent on the total amount of fluid in which it is injected into the animals. During a period up till eight weeks after immunization, the animals given injections of undiluted toxoid are less immune than those immunized with diluted toxoid. The experiments of Timmerman and Brandwijk make it doubtful whether this condition remains unaltered at a later period after the immunization.

FROM THE AUTHORS' SUMMARY.

STAPHYLOCOCCIC TOXOID IN THE TREATMENT OF DIABETES. R. S. WALE and K. MADDERS, Brit. J. Exper. Path. **17**:279, 1936.

The naturally occurring staphylococcic antitoxin is equal in diabetic and normal persons. Diabetes is not influenced by an injection of staphylococcic toxoid, although the same increase in titer of the antitoxin is produced in diabetic as in normal persons. Staphylococcic lesions were not sufficiently common among the diabetic subjects for a trial of their treatment by toxoid to be made.

FROM THE AUTHORS' SUMMARY.

THE IMMUNOLOGIC RELATIONSHIP BETWEEN KIKUTH'S CANARY VIRUS AND FOWLPOX. F. M. BURNET and D. LUSH, Brit. J. Exper. Path. **17**:302, 1936.

The viruses of fowlpox and Kikuth's canary disease can be accurately titrated by the pock-counting method on the chorio-allantoic membrane. Cross-neutralization tests indicate that the two viruses, though not identical, are serologically very closely related. There is no cross-reaction with the virus of vaccinia.

FROM THE AUTHORS' SUMMARY.

THE PURIFICATION OF STAPHYLOCOCCIC TOXOID. L. B. HOLT, Brit. J. Exper. Path. **17**:318, 1936.

Staphylococcus Wood 46 (and all other toxigenic strains of staphylococci which have been tested) will grow and produce potent toxin on a dialysate medium. The toxin thus produced can be converted into toxoid by formaldehyde. Such toxoids can be recovered by saturation with ammonium sulfate, by filtering off the precipitate formed and dialyzing it for two days. Dialysate medium, treated in the same way as toxoid, failed to give a positive reaction for protein. Toxoid prepared from a medium dialysate and purified by saturation with ammonium sulfate and dialysis of the precipitate is free from all the nitrogenous constituents of the original medium, and apart from some "water-soluble carbohydrate derived from the agar," the purified toxoid contains only material derived from the result of bacterial activity. This method of preparing and purifying staphylococcic toxoid (α antigen) has been used many times on a large scale. Toxoids prepared by this method have been found not inferior antigenically to those prepared on the routine medium and not purified with ammonium sulfate. The antigenic value and other properties of purified toxoid prepared in this manner, such as its relative stability and its liability to induce reactions when injected into patients, will be the text of a later communication.

FROM THE AUTHOR'S SUMMARY.

THE VI ANTIGEN OF B. TYPHOSUS. R. C. ROBERTSON and H. YU, J. Path. & Bact. **43**:191, 1936.

Vi antigen is not primarily correlated with the virulence of Bacillus typhosus or with the O antibody-resistant properties of the organism. Vi antibody is a protective substance in that it induces passive immunity in mice.

FROM THE AUTHORS' SUMMARY.

THE COMPLEMENT FIXATION TEST IN WEIL'S DISEASE. A. W. POT and C. G. J. DORNICKX, J. Path. & Bact. **43**:367, 1936.

The test is reliable and easy in performance and interpretation. The results are certainly not inferior to those of the agglutination and lysis tests.

FROM THE AUTHORS' SUMMARY.

HEMOLYTIC STREPTOCOCCI AND ANTISTREPTOCOCCIC SERUMS. H. SCHMIDT, Ztschr. f. Immunitätsforsch. u. exper. Therap. **87**:1, 9, 17, 177 and 268, 1936.

Schmidt set himself to devise a method for the estimation of the antifibrinolytic properties of antistreptococcic serums. He confirmed the observation that practically all hemolytic streptococci from human sources dissolve human fibrin, that the lytic property is present in the culture medium and is filtrable, that this property is not strictly species specific, for occasionally streptococci of animals dissolve human fibrin to some extent and vice versa. The preparation of the reagents (plasma, fibrinogen, thrombin, fibrinolysin) and the technic are described in detail. In the second article, he outlines the procedure for the determination of the antifibrinolytic properties of antistreptococcic serums, and lays down the minimum requirements. In the third article, he confirms the observation reported by J. Weld concerning the extraction of hemotoxin from hemolytic streptococci with serum. Schlueter and Schmidt found that serums from different species but no other fluids were suitable. It was possible to establish that other fluids removed the hemotoxin from the bacteria but were not able to preserve the extremely labile substance. Sharp quantitative relations between the bacteria and the serum must be observed. The effects of the extracted hemotoxin on mice, rabbits and guinea-pigs are described. No quantitative relation was found to exist between the hemotoxin and the pathogenicity of the streptococci, but such a relation was apparent between their ability to form hemotoxins and their ability to form hemolysins for rabbit red blood cells. That there was no strict specific-

ness of the fibrinolytic ability of streptococci but marked quantitative differences between cocci of human and animal origin was shown in the fourth article. Considerably larger amounts of lysin were necessary for the lysis of heterologous than for that of homologous fibrin. In general, streptococci of animals showed less lytic ability than those of man. There was no evidence of strict species specificity for the thrombin required for the reaction, but homologous thrombin was as a rule more efficacious. That there is no absolute regularity was evidenced by the occasional failure of streptococci of animal origin to dissolve the homologous fibrin. There is no strict parallelism between pathogenicity of streptococci and fibrinolysis in vitro, as evidenced by the failure of a streptococcus to dissolve the fibrin of mice for which it was highly virulent. In the final article, the antigenicity of the fibrinolysin in immunized horses the serum of which acquired antifibrinolytic properties was demonstrated in vitro. Following streptococcic infections in man there is observed a similar antibody. In vitro absorption of the antifibrinolysin was accomplished with the fibrinolysin but not with the streptococci. The fibrinolysin is best obtained in serum-free culture medium containing dextrose. It can be prepared as a dry powder and can be kept for a very long time.

I. DAVIDSOHN.

AUTO-AGGLUTINATION. P. NEUDA, Ztschr. f. Immunitätsforsch. u. exper. Therap. **86**:391, 1935.

The ability of some serums to agglutinate their own erythrocytes as well as those of all other human blood groups, including the O group, at icebox and at room temperature was found in various conditions but mainly in syphilis, cirrhosis of the liver and cancer. In fresh serum auto-agglutination is less marked than in rapidly inactivated serum, while incubation for twenty-four hours at 37 C. destroys the auto-agglutinins and at the same time imparts to the serum the ability to inhibit iso-agglutination when it is added to the serum of the opposite blood group. This inhibitory property is specific for the blood group and is due to activation of the blood group substance as a result of the incubation. The blood group O represents the species-specific factor that is present in all blood groups either alone as in group O or in addition to the group properties A and B. Neuda suggests the term "I" for the species-specific agglutinogen and the term "i" for its corresponding agglutinin, which is identical wth the auto-agglutinin (the so-called cold agglutinin, pseudo-agglutinin). The lowered auto-agglutinating ability of the fresh serum, according to Neuda, is due to interference by complement. When the auto-agglutinins were removed by specific absorption, the titer of the complement was frequently elevated. There was no difference noted in the titer of iso-agglutinins between the rapidly inactivated serum and the serum that was incubated for twenty-four hours, while the latter procedure tended to elevate the titer of hetero-agglutinins.

I. DAVIDSOHN.

Tumors

BENIGN HEPATOMA IN MICE OF THE CBA STRAIN. L. C. STRONG and G. M. SMITH, Am. J. Cancer **27**:279, 1936.

Fourteen cases of solitary benign hepatoma have been found in representatives of the CBA strain. This condition is probably genetic in its origin. The neoplastic condition may be related to a disturbance in the hepatic vascular or duct system.

FROM THE AUTHORS' SUMMARY.

THE CANCER FAMILY OF WARTHIN. I. J. HAUSER and C. V. WELLER, Am. J. Cancer **27**:434, 1936.

The family first reported by A. S. Warthin in 1913 now presents 43 primary carcinomas in 41 of a total membership of 305. Since only 174 members have attained the age of 25 years, this gives a cancer incidence of 23.6 per cent in those

reaching that age. In two branches of the family cancer has never appeared. The anatomic location of the primary lesion is more significant in this family than the total incidence; 26 carcinomas have occurred in the gastro-intestinal tract and 15 in the endometrium. While no conclusions as to the mendelian implications appear to be justified, this family provides very strong presumptive evidence for an inheritable organ-specific predisposition to carcinoma.

FROM THE AUTHORS' SUMMARY.

THE INFLUENCE OF HORMONES ON HYPERPLASIA AND NEOPLASTIC GROWTH OF THE BREAST IN WHITE RATS. J. HEIMAN and O. F. KREHBIEL, Am. J. Cancer **27**:450, 1936.

The variations occurring in transplanted benign fibro-adenoma of the rat's breast cannot be attributed solely to variations in the implant. Endocrine factors in the host probably contribute to these changes. The increase in the rate of growth and number of takes of the tumor in male castrates bears some relation to endocrine imbalance. The decrease in the rate of growth and number of takes in female castrates may also bear some relation to endocrine imbalance. Antuitrin S (the anterior pituitary-like gonadotropic hormone from the urine of pregnant women) and theelin (an estrogenic substance) in combination increased the incidence of the tumor in both male and female castrates. Antuitrin G (a preparation of the anterior lobe of the pituitary gland said to contain the growth hormone) antuitrin S or theelin injected singly or in combination produced definite increase in hyperplasia of the breast, leading to benign fibro-adenoma. After growing in young sexually immature rats, transplanted fibro-adenoma becomes cellular fibroma or sarcoma. After passing through several generations, cellular fibroma or sarcoma retains the same morphologic traits, even when implanted in adult or old animals.

FROM THE AUTHORS' SUMMARY.

LIPOSARCOMA PRODUCED BY 1, 2-BENZPYRENE. C. D. HAAGENSEN and O. F. KREHBIEL, Am. J. Cancer **27**:474, 1936.

The development of liposarcoma as a result of subcutaneous injections of 1, 2-benzpyrene adds another type to the several forms of sarcoma which have been induced by means of 1, 2, 5, 6-dibenzanthracene, 1, 2-benzpyrene and related chemicals. Evidence is rapidly accumulating which indicates that these pure hydrocarbons possess not only an extraordinary power of inducing cancer but the power of inducing it in a great variety of tissues. Liposarcoma is an unusual form of neoplasm. Its rarity may be explained on the assumption that fat is an inactive tissue with very little capacity for growth. Yet the stimulating action of benzpyrene is evidently so great that it can induce malignant change even in this relatively inactive tissue. It should be noted that, according to the experience of Haagensen and Krehbiel, liposarcoma has been the least frequent type of sarcoma induced by 1, 2-benzpyrene. In mice this type of tumor has been exceedingly infrequent. Among 336 mice that received multiple subcutaneous injections of benzpyrene and survived as long as four months (the average interval of time required for the development of sarcoma in the present series) 206 showed sarcoma. These sarcomatous mice bore a total of 233 growths of various types, and only one was a liposarcoma.

FROM THE AUTHORS' DISCUSSION.

THE FATE OF INTRAVENOUSLY INJECTED TUMOR CELLS. S. WARREN and O. GATES, Am. J. Cancer **27**:485, 1936.

The results of intravenous injections of artificial and natural suspensions are compared. Walker carcinoma 256 in the Sloniker strain of white rat was used. The uninjured cells in natural suspension give earlier and more numerous pulmonary tumor nodules. The mechanism of metastasis is the same with both

inocula. Blood has no toxic effect on tumor cells. Involvement of extravascular tissue rarely occurs by direct penetration of the arteriolar wall but usually by growth through the less resistant capillary wall. Hyaline thrombi appear early and disappear early without organization. There is no reaction of the endothelium to tumor tissue. The most important factor in metastasis is the potentiality for growth of the individual cells. FROM THE AUTHORS' SUMMARY.

HEMOGLOBIN LEVELS CORRESPONDING TO VARIOUS DEGREES OF SUSCEPTIBILITY TO SPONTANEOUS TUMORS. L. C. STRONG, Am. J. Cancer **27**:500, 1936.

There is a precocious drop in the level of hemoglobin in mice which are known to be genetically more susceptible to the development of spontaneous carcinoma as compared with mice which are more resistant. This defect is probably hereditarily determined. The drop may reflect a premature aging involution. It is possible to work out a hypothesis for the origin of cancer by taking into consideration (*a*) the contributions of cell respiration and allied phenomena of oxidation-reduction systems, (*b*) the physiologic effect of carcinogenic agents and (*c*) a genetic analysis of that part of susceptibility and resistance to spontaneous carcinoma which is hereditarily determined. FROM THE AUTHOR'S SUMMARY.

THE INFLUENCE OF BLOCKAGE OF THE NIPPLE IN MAMMARY TUMOR IN THE MOUSE. E. FEKETE and C. V. GREEN, Am. J. Cancer **27**:513, 1936.

Blockage of the mammary ducts with resulting stagnation of milk was influential in determining the sites and the dates at which mammary tumors appeared in a genetically susceptible strain but did not in itself cause the tumors, since it was unable to overcome the hereditary resistance in animals of a strain in which such tumors normally do not develop.

EXTRACHROMOSOMAL INFLUENCE IN TUMORS IN MICE. W. S. MURRAY and C. C. LITTLE, Am. J. Cancer **27**:516, 1936.

Mammary tumors of epithelial origin are transmitted largely by means of extrachromosomal influences. Some other types of tumors do not follow this law.

THE EVIDENCE FOR AN ENDOCRINE FACTOR IN MAMMARY TUMORS. H. C. TAYLOR JR., Am. J. Cancer **27**:525, 1936.

Any attempt to define the stage to which clinical and experimental work has carried the theory that a cause for cancer of the breast is to be found in the endocrine gland is difficult and is certain to receive little approval. The following points are nevertheless offered as perhaps the most important. The ovarian hormone is essential for the development and preservation of the epithelium of the mammary gland. Without it there is no tissue on which any carcinogenic agent may act. This is the most obvious reason why cancer of the breast does not develop in animals early castrated or in untreated male mice. The development of cancer of the breast in mice after injections of large quantities of estrogenic hormone may be brought about in several ways: (*a*) by a direct carcinogenic action comparable with that of various derivatives of tar; (*b*) by an increase in the normal physiologic impulse to proliferation until it produces atypical structures; (*c*) by an abnormal activtiy of the cells that produce the secretions which provide the carcinogenic factor. Human mammary tumors are also dependent on the ovaries at least to the extent that the normal tissue from which the tumors arise is provided by the ovarian hormone. Ovarian function is apparently essential for the common types of chronic mastitis and fibro-adenoma, the development of which is practically limited to the years of mature sexual life. This is not true of carcinoma, which may appear long after the menopause. With the neoplastic disease once established, a marked response to variations in glandular function, such as those incident to pregnancy and the menopause, is noted in chronic mastitis and fibro-

adenoma. A moderate reaction to these changes is observable in carcinoma in some cases. Some evidence of glandular dysfunction can be found in certain cases of chronic mastitis, but hormonal states comparable to those necessary to produce mammary carcinoma in mice by the injection of estrogenic hormone are unknown in women. There is no clinical evidence yet that any specific endocrine dysfunction is the cause of cancer of the human breast. FROM THE AUTHOR'S SUMMARY.

THE RELATION OF FUNCTIONAL ACTIVITY TO MAMMARY CARCINOMA IN MICE. H. J. BAGG, Am. J. Cancer **27**:542, 1936.

The functional activity of the mammary gland is related to the production of spontaneous tumors of the mammary glands in certain strains of mice. Apparently internal factors of a hormonal nature (probably ovarian in this case) and possibly the chemical irritation of retained mammary secretions bear a causative relation to the onset of mammary carcinoma. Rapid breeding and nonsuckling (the so-called functional test) have aided in detecting in distinctly low tumor strains, especially C57, mice with a constitution favorable to the growth of tumors of the mammary glands. Conversely, the failure to produce such a tumor even after a severe functional test may indicate an animal with a constitution unfavorable to the growth of the tumor. Selective breeding combined with the functional test may make it possible to standardize still further high tumor or low tumor strains. The process of rapid breeding and prevention of suckling has apparently lowered the threshold for the growth of spontaneous tumors of the mammary glands in hybrid female mice, so that a so-called extrachromosomal influence, if present, is not shown in the results so far obtained. A spontaneous tumor arising in low tumor strain C57 has given very poor transplants in mice of the same strain; in the instances in which the results were positive, it has grown slowly. It has grown in hybrid mice, one parent of which was from its strain of origin, but it has failed to grow in two other pure strains. FROM THE AUTHOR'S SUMMARY.

RENAL ADENOMA. A. J. TRINKLE, Am. J. Cancer **27**:676, 1936.

Adenoma of the kidney occurs most frequently in adults over 50 years of age, most commonly in kidneys the seat of vascular disease. Papillary adenoma arises from the epithelium of hyperplastic tubules and cysts. The hyperplastic tubules and cysts are found in areas of vascular occlusion, and their development appears to be dependent on reestablishment of a blood supply. Papillary adenoma in some of its structural variations may be similar to hypernephroma. Transition forms of papillary adenoma have been described in which a structure indistinguishable from that of hypernephroma is present. A similarity in structure has been pointed out between early hypernephroma and extensive adenoma in some cases. The available evidence seems to justify the conclusion that hypernephroma may develop from papillary adenoma. FROM THE AUTHOR'S SUMMARY.

MULTIPLE HEREDITARY HEMANGIOBLASTOMA OF THE NERVOUS SYSTEM. P. M. LEVIN, Arch. Neurol. & Psychiat. **36**:384, 1936.

In a woman aged 19 who presented clinically a tumor of the posterior fossa, Lindau's disease (hemangioblastoma of the cerebellum with possible involvement of the retina) was diagnosed. At operation, a cyst of the left cerebellar hemisphere and a tumor of the left tonsil and of the spinal cord at the level of the first cervical segment were found. Part of the left tonsil which was excised proved microscopically to be hemangioblastoma. The family history, not verified, revealed that the patient's father and an aunt had tumors. G. B. HASSIN.

EXPERIMENTAL PRODUCTION OF MALIGNANT GROWTHS IN MICE BY ESTROGENIC CHEMICALS. W. U. GARDNER and others, J. A. M. A. **107**:656, 1936.

Estrogenic hormones have been given to 126 mice of three inbred strains for periods of four months or more. In 28 mice one or more mammary carcinomas,

and in 7 mice spindle cell sarcomas, have developed as local reactions in relation to retained oil cysts at the sites of injection. Mammary cancers have developed in male mice receiving theelin, equiline benzoate, keto-estrin benzoate and hydroxy-estrin benzoate. Mammary tumors have occurred in 2 of 3 females of the relatively tumor-resistant CBA strains. FROM THE AUTHORS' SUMMARY.

PAPILLOMA AND CARCINOMA OF THE BLADDER IN DYE WORKERS. G. H. GEHRMANN, J. A. M. A. **107**:1436, 1936.

Papilloma and carcinoma of the urinary bladder are caused by long exposure to certain nitro and amino compounds. The average time of exposure necessary to produce tumors is twelve years. Tumors may be single or multiple, benign or malignant. All benign tumors should be considered potentially malignant. Early diagnosis is essential, and periodic cystoscopic examination is the only safe method of detecting these tumors early. Proper control of the dye works and medical supervision will eliminate the incidence of these tumors.

FROM THE AUTHOR'S SUMMARY.

A STUDY OF THE INCIDENCE OF CANCER OF THE LUNG AND LARYNX. N. M. KENNAWAY and E. L. KENNAWAY, J. Hyg. **36**:236, 1936.

The death certificates for males dying of cancer of the lung and of the larynx in England and Wales for the years 1921-1932, numbering 18,280, were investigated. In metal grinders the incidence of cancer of the lung is two and a quarter times that in the general population. In occupations in which there is exposure to road dust, the incidence of cancer of the lung and of cancer of the larynx is high. Those exposed to coal gas and tar and those engaged in the preparation and sale of tobacco show increased prevalence of cancer of the lung. Motor drivers have a normal liability to cancer of the larynx. The factors which lead to silicosis are not active in producing cancer of the lung or of the larynx.

VIRUS IN A NONFILTRABLE TAR SARCOMA OF THE FOWL. C. H. ANDREWES, J. Path. & Bact. **43**:23, 1936.

A nonfiltrable, or at any rate hitherto unfiltered, tar-induced fowl sarcoma grew for a time when inoculated into adult pheasants. Usually regression occurred after one or two weeks, but in two pheasants the tumors reached very large sizes and continued to grow for six or seven weeks before regressing. Precipitin tests appeared to show that the tumor in one of these birds consisted of pheasant cells. All the pheasants inoculated with the tar tumor produced antibodies which would neutralize the virus of Rous sarcoma 1. Such antibodies have never been found in normal pheasant serums and were not induced by immunization of pheasants with normal fowl embryo. Other evidence is produced that the neutralization was caused by true antiviral and not by antifowl antibodies. The conclusion is drawn that the Sheffield tar fowl sarcoma contains a virus, though this cannot be directly demonstrated by infecting with filtrates.

FROM THE AUTHOR'S SUMMARY.

BONE SARCOMA IN OSTEITIS DEFORMANS. G. C. PARENTI and H. LÜDEKE, Virchows Arch. f. path. Anat. **296**: 200, 1936.

Following Pick, Schmorl and others, the metapoietic malacias of bone are subdivided into generalized osteitis fibrosa (Recklinghausen's disease), localized osteitis fibrosa and osteitis deformans (Paget's disease). The authors claim that there is no authentic record of sarcoma developing in osteitis fibrosa. But the literature contains reports of thirty-one cases of sarcoma in osteitis deformans. Their survey of the literature leads them to conclude that this association is not a matter of coincidence, but that the osseous changes characteristic of Paget's disease lead to sarcoma. The case reported by them was that of a 67 year old physician who had had osteitis deformans for thirty-five years. Spontaneous

fracture of the tibia necessitated amputation, which was followed thirty-three days later by death. Examination of the involved tibia revealed, in addition to the characteristic changes of osteitis deformans of long standing, osteogenic sarcoma. In addition to the main tumor in the lower third of the tibia, there were a number of smaller ones separate from each other and from the large tumor, a finding which leads the authors to postulate a possible multicentric origin of sarcoma in osteitis deformans.

In the American literature a multitude of sins and shortcomings may be covered by the statement "Permission for necropsy could not be obtained." It is rather unexpected to find in a German article the sentence *"Eine Sektion durfte nicht vorgenommen werden,"* especially when the candidate for necropsy was a physician.

O. T. SCHULTZ.

TUMOR OF THE PINEAL BODY. E. BENECKE, Virchows Arch. f. path. Anat. **297**: 26, 1936.

A 16 year old boy had complained for several years of headache, polydipsia and polyuria. The body size and configuration were normal for the age. The penis was of normal size. The testes felt atrophic. Death occurred in coma, with convulsive contractions of the extremities, rapidly rising temperature and respiratory paralysis. Necropsy revealed a midline tumor of the pineal region, with the dimensions of 3.2 by 4 cm. on the cut surface. The tumor had filled the third ventricle. Except in an area where the tumor had invaded the brain, it was sharply delimited and encapsulated. The neoplasm was a teratoma with derivatives of the three germ layers. It probably originated from pluripotent cells of the primitive streak. The invasive part of the tumor consisted of pineal tissue with an indistinct alveolar arrangement. The seminal tubules of the testes were hypoplastic, but the interstitial tissue was hyperplastic. In this case the macrogenitosomia that has been associated with pineal tumors was not evident.

O. T. SCHULTZ.

PAPILLOMATOSIS AND CARCINOMA OF THE PANCREATIC DUCT SYSTEM. G. HABÁN, Virchows Arch. f. path. Anat. **297**:207, 1936.

A woman aged 70 years was admitted to a hospital because of profuse hematemesis and sudden severe pain in the upper part of the abdomen. She had marked secondary acute anemia. The urine contained 2.8 per cent sugar. At necropsy the pancreas was sclerotic and revealed active inflammation with interstitial cellular infiltration. The intrapancreatic ducts were increased in number and were dilated. Their epithelium was papillomatous and in many places had undergone carcinomatous transformation. Inflammatory involvement of a branch of the anterior pancreaticoduodenal artery had led to aneurysmal dilatation of the vessel and erosion into one of the dilated ducts. The inflammatory process in the parenchyma and islets had led to diabetes.

O. T. SCHULTZ.

Technical

DIAGNOSIS OF GONOCOCCIC INFECTIONS BY THE CULTURAL METHOD. A. D. LEAHY and C. M. CARPENTER, Am. J. Syph., Gonor. & Ven. Dis. **20**:347, 1936.

A modification of McLeod's cultural method for the diagnosis of gonococcic infections is described. The method consists in making cultures on "chocolate" agar, prepared with a Douglas agar base, and incubating them at 34 C. and 37 C. in an atmosphere of air reenforced in its carbon dioxide content to approximately 10 per cent. The oxydase test, employing a 1 per cent aqueous solution of dimethylparaphenylenediamine hydrochloride, is used to identify colonies of the gonococcus in mixed cultures. By this technic 130 cultures of the gonococcus were isolated, representing 43 per cent of the 302 specimens submitted for examination from 138 patients. The cultural method resulted in the discovery of 10 per

cent more cases of gonococcic infection than were discovered by the smear method alone. The percentage was much higher when only specimens from the lower part of the birth canal and from prostatic secretions were considered. The incubation of cultures in an atmosphere of air reenforced in its carbon dioxide content to approximately 10 per cent resulted in the isolation of 15 per cent more cultures of gonococci than were recovered from duplicate cultures incubated in air under conditions that were otherwise identical. The oxydase test detected 21, or 14 per cent, of 146 cultures of the gonococcus that would have been reported negative had direct inspection alone been relied on.

FROM THE AUTHORS' SUMMARY.

AN INEXPENSIVE MEDIUM FOR THE TUBERCLE BACILLUS. SAM WONG and JOHN WEINZIRL, Am. Rev. Tuberc. **33**:577, 1936.

To avoid the high cost of asparagine, which is used in Long and Seibert's medium, the authors tried the medium described by Henley and LeDuc (*Am. Rev. Tuberc.* **22**:568, 1930) containing ammonium malate, but not with satisfactory results. Using these two mediums as a basis, they prepared an inexpensive medium suitable for the production of tuberculin in large quantities at a third of the cost of the medium of Long and Seibert. A maximal growth of Mycobacterium tuberculosis, H 37, in the new ammonium malate medium which has 1 per cent dextrose added, may be obtained in four weeks; in other words, about the same weight of organisms may be obtained in approximately half of the time usually required. The same amount of tuberculin can be obtained with the dextrose-malate medium as with the asparagine medium but in approximately half the time. The medium consists of malic acid, 3 Gm.; ammonium hydroxide (10 per cent solution), 12 cc.; ammonium citrate, 5 Gm.; monopotassium acid phosphate, 6 Gm.; magnesium sulfate, 1 Gm.; ferric ammonium citrate, 0.05 Gm.; glycerol, 50 cc.; distilled water to make 1,000 cc.; dextrose solution, to be added after sterilization, 10 Gm. The p_H initially should be 6.8 to 7 and finally about 7. The medium is autoclaved at 20 pounds (9 Kg.) for fifteen minutes. A 20 per cent solution of chemically pure dextrose is sterilized in test tubes to facilitate its introduction into the flasks. If it becomes necessary to readjust the hydrogen ion concentration after autoclaving, the medium must be titrated to p_H 7.4 and autoclaved again at 20 pounds for fifteen minutes. Reautoclaving does not alter the usefulness of the medium.

H. J. CORPER.

A TEST FOR INGUINAL LYMPHOGRANULOMA. A. W. GRACE and F. H. SUSKIND, J. A. M. A. **107**:1359, 1936.

Standardized lymphogranulomatous mouse brain is the most suitable antigen for use in the routine performance of the Frei test.

HANGING DROP CULTURE FOR DIAGNOSIS OF TINEA INFECTIONS. F. L. BLUMENTHAL and J. S. SNOW, J. A. M. A. **107**:1367, 1936.

The hanging drop culture is useful in the diagnosis of tinea infections. It is dependable and simple and requires only a short time.

MYELIN SHEATH STAINING METHOD. F. FEYRTER, Virchows Arch. f. path. Anat. **296**:644, 1936.

A simple method for staining myelin sheaths is described. Frozen sections of tissues fixed in a 10 per cent solution of formaldehyde or in Orth's solution and washed in water are spread on a slide and stained in a solution made up as follows: thionine, 1 Gm.; tartaric acid, 0.5 Gm., and distilled water, 100 cc. After five minutes a cover glass is placed on the section, the excess of stain is absorbed by filter paper held at the edge of the cover glass, and the latter is ringed. Myelin sheaths are stained red. Fehrter claims that the metachromatic staining is limited to the myelin sheaths and the derivatives of the Schwann cells, which stain in varying shades of red.

O. T. SCHULTZ.

Society Transactions

PATHOLOGICAL SOCIETY OF PHILADELPHIA

Jan. 14, 1937

ESMOND R. LONG, *President*

HERBERT L. RATCLIFFE, *Secretary*

MYCOTIC ANEURYSM AND SUBACUTE BACTERIAL AORTITIS, ASSOCIATED WITH SEVERE CHRONIC RHEUMATIC HEART DISEASE. ROBERT S. CREW.

A Negro boy of 17 entered the Philadelphia General Hospital Nov. 15, 1936, complaining of pain over the heart and in the left arm. In December 1934, while at work, he suddenly experienced a sharp pain over the precordium, which radiated down the inside of the left arm. After fifteen minutes' rest, the pain disappeared spontaneously. Since that time he has frequently had similar attacks of pain. Simultaneously, palpitation and dyspnea on moderate exertion developed, and because of increasingly severe precordial pain induced by slight exertion he has remained in bed since Nov. 8, 1936. Prior to the present illness he had had frequent attacks of sore throat, and tonsillectomy was done at the age of 13. This was followed by a typical attack of acute rheumatic fever.

The boy was rational and well nourished, with a normal temperature and respiratory rate. The pulse was forceful, of the Corrigan type, with a rate of 120 per minute. The blood pressure was 128 systolic and 40 diastolic. There were marked venous pulsations in the forehead and neck. Capillary pulsation was present; a systolic thrill was palpated in the suprasternal notch and over the precordium, and a diffuse forceful apex beat was visible in the midaxillary line in the fifth interspace. The heart was shown by x-ray picture and orthodiagram to be greatly enlarged, the right border extending 6 cm. and the left border 12.2 cm. from the midsternal line. The heart sounds were regular and forceful. The first sound at the apex was replaced by a blowing systolic murmur, transmitted to the axilla, and a presystolic rumble obscured the second sound. A rough diastolic and a softer systolic murmur were audible at the aortic area. The pulmonic second sound was accentuated with the quality of snapping. An electrocardiogram showed deeply inverted T waves in leads I and II, indicating severe myocardial change. The lungs were clear, and peripheral edema was absent. The results of urinalysis, the Kahn test and chemical tests of the blood were negative. Blood cultures remained sterile.

Beginning November 19, the patient began to show elevation of temperature, which ranged from 98 to 104 F., with pulse beats from 80 to 130 per minute and respirations from 20 to 40. On November 22 a precordial friction rub was noted at the fourth interspace in the anterior axillary line. The patient grew progressively weaker and died December 8.

Postmortem Examination.—The pericardial sac contained 800 cc. of slightly cloudy amber fluid with a specific gravity of 1.019, and the visceral pericardium around the root of the great vessels showed injection and was granular. The heart weighed 800 Gm., and all the chambers and valve rings were greatly dilated. The muscle was hypertrophied, the left ventricular wall measuring 25 mm. and the right ventricular wall 9 mm. The free edges of the mitral leaflets and the mitral chordae tendineae were firm and thickened. The aortic leaflets were shortened, with the free edges rolled and thickened. The left anterior leaflet contained a fenestration 3 mm. in diameter, with its margins rolled and thickened, possibly the result of a healed ulcerative lesion. The commissures were not widened. Just above the right anterior leaflet, in the root of the aorta, involving the sinus of Valsalva, there was a flattened sacculated aneurysm 3 cm. in diameter,

with smooth, rounded margins and an apparently endothelialized lining. Adherent to the inferior margin there were two small friable red-gray vegetations; a small crust formed the margin of the upper sector.

Microscopic examination of the heart muscle revealed evidence of previous rheumatic infection, viz., a pericoronary mat of frayed collagen. In addition there was superimposed acute nonsuppurative interstitial myocarditis. The vegetations along the margin of the aneurysm contained numerous cocci in pairs and short chains, resembling streptococci morphologically.

Microscopic sections taken through the base of the aneurysm showed an endothelialized lining, with the internal elastic lamella split into layers, clumped and extensively destroyed; the elastic fibrillae of the media were largely lost, a few isolated patches persisting. Arranged around non-nucleated fibrillar material and often around small blood vessels were cell masses suggesting Aschoff bodies, including large monocytoid cells, a few being giant forms, with a sprinkling of lymphocytes and neutrophils; swirls and fasciculi of fibroblasts lay in the background. There could be little doubt of this being evidence of active rheumatic disease in the aorta. Elsewhere the inflammatory reaction was nonspecific in character.

The pathogenesis of the aneurysm is open to some question; such a lesion developing on the basis of pure rheumatic aortitis has not been described, and it probably should be regarded as of the so-called mycotic type, especially when found in the presence of a perforated aortic leaflet. The case clinically was one of chronic rheumatic heart disease with superimposed subacute bacterial endocarditis. The rheumatic valvular lesions were pronounced, yet the bacterial growth was confined exclusively to the aorta. The heart did not show recrudescence of the rheumatic inflammation; the aorta did. Hence, this case lends support to von Glahn's contention (presented before this society several years ago) that subacute bacterial endocarditis is ingrafted not on an inactive, post-rheumatic lesion but on a recurrent rheumatic process.

BRONCHIOGENIC CARCINOMA SIMULATING PULMONARY TUBERCULOSIS, WITH METASTASES TO THE ARTERIAL MESOCARDIUM. O. NORRIS SMITH.

This case was unusual from two standpoints: First, the metastases were confined primarily to the adventitia of the great arteries normally covered by visceral pericardium. Second, the diagnosis of pulmonary tuberculosis was made by the clinicians, substantiated by the roentgenologists and confirmed on gross postmortem examination not only by myself but by one of the senior members of our department.

A 47 year old Jewess contracted pleurisy, unproductive cough and chills in May 1936. There was temporary alleviation of the symptoms the following month. During the summer a continuous cough, anorexia, malaise and later hoarseness were paramount symptoms. On admission to the hospital in December, she was acutely ill, emaciated, cyanotic and incessantly coughing. She presented clinical evidence of right apical cavitation with râles. She was not anemic, and examinations of the sputum revealed no tubercle bacilli, but there was neutrophilic leukocytosis (25,000 cells), and the red cell sedimentation rate was slightly accelerated. She succumbed on the following day rather unexpectedly, exhibiting marked terminal cyanosis.

At the apex of the right lung, a zone of dense fibrous adhesions covered a walnut-sized ulcerating cavity. Throughout the upper lobe of this lung and to a lesser extent in the lower lobes, the septums containing the lymphatic vessels were conspicuous and were sparsely studded with minute gray nodules resembling in every detail miliary tubercles. Larger but similar nodes were present beneath the pleura of the lung and the diaphragm, also in the parietal pericardium. Pulmonary edema was marked. Mediastinal lymphadenopathy was not conspicuous. The heart was not enlarged, and the epicardium grossly was smooth and glistening, excepting that portion which formed the adventitia of the great

arteries. Extending from the origin of the aorta and pulmonary artery to the point of reflection of the parietal pericardium, a distance of several centimeters, a soft fungating red mass presented a sufficiently granular surface to be likewise considered tuberculous, though unique in distribution and atypical in appearance.

Histologic sections demonstrated that all the changes were attributable to a bronchiogenic carcinoma, which was widely distributed through the subpleural and peribronchial lymphatic channels, with numerous nodular excrescences. Metastases were confined to the lung, the diaphragm, the mediastinal lymph nodes and the pericardium. In the latter they not only formed the fungating mass described but also ramified throughout the lymphatic vessels.

Other pathologists more experienced in tuberculosis acknowledge deception by pulmonary dissemination of bronchiogenic carcinoma, and it is not unlikely that clinicians and roentgenologists encounter such mimicry more frequently.

Cultivation and Classification of Yeastlike Fungi. Carl J. Bucher.

Of most value in identifying the mycotorulae are the morphology of the giant colony, the character of the blastospores and the arrangement of the blastospores on the hyphae, particularly of the terminal one. For this purpose the most serviceable culture mediums are: a thin slant of Sabouraud's dextrose agar in a thin-walled test tube, permitting direct microscopic study of the fungus; potato water and beer wort, in which hyphae develop readily, and slanted Sabouraud's dextrose agar in ordinary small-mouthed flat medicine bottles of pint capacity, for developing the giant colony. Drying of the medium is prevented, and photographs are easily made, at any stage of growth. Liquefaction of gelatin, fermentation of carbohydrates and serologic tests are of doubtful value in the identification of the fungi. Tests for pathogenicity should be made on a number of animals before conclusions are drawn.

Of the more important classifications of the anascosporous yeastlike fungi producing hyphae, that of Langeron and Talice is of the most service to clinical mycologists at present, even though it cannot be completely accepted. Until there is better agreement among mycologists, it seems best to describe newly isolated organisms in detail and to fit them tentatively into this classification.

Effects of Several Chemical Agents on the Testes of Some Experimental Animals. W. C. Hueper.

During studies on the organotoxic effects of a large series of chemical agents, testicular and epididymic degenerations were observed in experimental animals (mice, rats, rabbits, cats, pigeons) treated with some of these substances (chloroprene, carbon disulfide, hydrogen sulfide, alkyl mercury, betanaphthylamine, etc.). The lesions usually occurred after administration of a single lethal or slightly sublethal dose or after repeated introduction of relatively large, toxic doses over a prolonged period. There existed marked variability in the sensitivity of the germinative epithelium of the tubules of the same testis, of the testes of different animals of the same species and of the testes of animals from different species. The testes of the rats and to a lesser degree also those of the mice showed more or less extensive intratubular calcifications of necrotic matter in an appreciable percentage of animals exposed. Mild, localized degenerative testicular lesions were observed in 15 per cent of a control series of ninety normal white rats.

Chemical Studies on Crystalline Proteins of the Virus of Tobacco Mosaic. W. M. Stanley.

A crystalline protein of high molecular weight, possessing the properties of the virus of tobacco mosaic, has been isolated from Turkish tobacco plants affected with this disease. The fact that the crystalline protein from many different batches of starting material has the same chemical composition, isoelectric point, optical rotation and biologic activity and that these properties

remain constant during many recrystallizations and following drastic fractional crystallization, the fact that it was found impossible to separate the activity from the protein by means of filtration through collodion or other types of filters or by centrifugation of the protein from solution under a variety of conditions, the fact that the absorption spectrum of the protein agrees essentially with the destruction spectrum of the virus activity, the homogeneity of the protein with respect to molecular size and iso-electric point, the isolation of the protein from plants distantly related to tobacco, the isolation of different proteins from plants diseased with different strains of the virus of tobacco mosaic and the fact that any change in the protein is accompanied by a change in the activity of the virus are all indications that the activity of the virus is a property of the protein. In view of the complete absence of any contradictory evidence, it is felt that the results justify the conclusion that this unusual protein of high molecular weight is the virus of tobacco mosaic.

NEW YORK PATHOLOGICAL SOCIETY

Anniversary Meeting, Jan. 28, 1937

N. CHANDLER FOOT, *President*

MILTON HELPERN, *Secretary*

TUBERCULOSIS OF THE MYOCARDIUM: REPORT OF TWO CASES. RUSSELL L. HOLMAN (by invitation) and JOHN J. HAWTHORNE (by invitation).

Within a period of ten days, two puzzling cases of cardiac disease were observed in patients admitted to the wards of the Presbyterian Hospital. Both patients died shortly after admission, one with a clinical diagnosis of arteriosclerotic heart disease and the other with a diagnosis of rheumatic heart disease. Necropsy revealed tuberculosis of the myocardium in each.

CASE 1.—An obese Irish widow of 72 years had a three months' history of progressive heart failure associated with brief fainting spells; she was admitted on July 24, 1935. The temperature was 99 F.; the pulse rate, 32 per minute; the respiratory rate, 18 per minute; the blood pressure, 135 systolic and 40 diastolic. The chief findings on physical examination were enlargement of the heart to the left and edema of the ankles. The Wassermann test of the blood was negative. The red blood cells were 3,900,000 and the white blood cells 15,200 per cubic millimeter; the differential white cell count showed 92 per cent polymorphonuclears and 8 per cent lymphocytes. An electrocardiogram revealed a ventricular rate of 40 and very small auricular waves with a rate of about 200 per minute. The diagnosis was complete heart block, left bundle branch block and auricular flutter. The patient lived only four days after admission and during this time had frequent periods of asystole lasting as long as three minutes. Death occurred in one of these attacks. The clinical diagnosis was arteriosclerotic heart disease, complete heart block and the Adams-Stokes syndrome.

At necropsy the peritoneal cavity contained 200 cc. of clear straw-colored fluid, and each pleural cavity held 100 cc. of similar fluid. The pericardium was everywhere smooth and glistening, and there was no excess of pericardial fluid. The heart weighed 480 Gm. About 1.5 cm. below the membranous portion of the interventricular septum was an irregular mass of dense gray translucent tissue in the midportion of the septum; this was irregular in outline, measured roughly 1 cm. in diameter and extended up to the endocardium of the left ventricle. The artery supplying this area arose from the anterior descending branch of the left coronary artery and was remarkably free from arteriosclerotic change, as were the other coronary arteries and the aorta. This area of apparent scarring amply explained the heart block. Outside this scarred area the myocardium was uniformly

grayish red and beefy, with here and there a few delicate grayish white streaks coursing through it. The wall of the left ventricle was hypertrophied, averaging 2 cm. in thickness. All the valves appeared normal.

The hillar node draining the upper lobe of the left lung contained a typical old calcified tuberculous lesion, measuring 3 mm. in diameter, but no old primary focus was found in the parenchyma of the lung. Some of the anterior superior mediastinal, periaortic, retroperitoneal, peripancreatic and right inferior cervical nodes were slightly enlarged. On the moist grayish white cut surface of these nodes could be seen numerous tiny faintly opaque dots. The cut surface of the thyroid gland, especially the right lobe, showed much scarring and numerous small circumscribed adenomas.

In the histologic section of the cardiac septum numerous tubercles were scattered about in abundant dense scar tissue. These tubercles were situated along blood vessels and lymphatics and were composed of loose infiltrations of plump epithelioid cells, lymphocytes and giant cells of the Langhans variety. In places, these tubercles and surrounding scar tissue encroached on Purkinje fibers. For histologic study two blocks were taken at random from the wall of each of the four chambers, and only in a section of the left ventricle were similar lesions found. More compact tubercles were present in the bronchial lymph nodes and peribronchial areolar tissue, in the mediastinal, inferior cervical and retroperitoneal lymph nodes and in the thyroid gland. Caseation was not seen in any of the tubercles. The lungs and other viscera were free from active tuberculosis. The only other incidental lesion of interest was a carcinoid of the terminal part of the ileum with microscopic metastases in the lungs. Several hours of painstaking search, including the employment of antiformin, failed to disclose acid-fast bacilli in any of the numerous sections of the heart and lymph nodes studied. Gram, methylene blue, Giemsa and Levaditi stains failed to reveal any organisms. The histologic appearance of the lesions and a comparison with similar cases reported in the literature justify the diagnosis of tuberculosis of the myocardium. However, the failure to find tubercle bacilli renders this diagnosis somewhat less certain.

Case 2.—A Negress aged 27 was admitted to the hospital Aug. 3, 1935, because of increasing dyspnea and orthopnea for three months, edema of the ankles, and productive cough for two weeks. Typical asthmatic attacks, usually initiated by exertion and increasing in frequency and severity, had also been noted during the past three months. The temperature was 98.6 F.; the pulse rate, 128 per minute; the respiratory rate, 44 per minute; the blood pressure, 100 systolic and 80 diastolic. The heart was moderately enlarged, and the sounds were of poor quality. There were occasional extrasystoles and double mitral murmurs. Edema of the ankles was present. The Wassermann test of the blood was negative. The hemoglobin was 110 per cent; the red blood cells numbered 5,750,000 per cubic millimeter. An electrocardiogram disclosed sinus tachycardia and ventricular premature beats. The patient died suddenly forty-eight hours after admission. The clinical diagnosis was active rheumatic carditis, chronic valvular disease, cardiac hypertrophy and chronic passive congestion of the lungs and liver.

At necropsy the pericardial surfaces were smooth and glistening; the pericardial sac contained about 50 cc. of straw-colored fluid. The heart weighed 400 Gm. Over the posterior surface of the heart were numerous yellowish white areas, varying in size from 1 to 5 mm. in diameter. These were slightly raised and covered with smooth epicardium. In the walls of the right auricle and left ventricle similar areas were found beneath intact endocardium. The papillary muscles of the mitral valve were partially replaced by soft grayish white tissue. Section of the myocardium, particularly that of the left ventricle, showed numerous similar areas scattered through its substance. Many of these measured as much as 1 cm. in diameter and were irregular in shape. On the endocardial surface of the left auricle, above the posterior mitral leaflet, was a raised wrinkled firm yellowish plaque, interpreted as an area of healed rheumatic endocarditis. All valves and coronary arteries appeared normal. The left auricle and left ventricle were

dilated and their walls moderately hypertrophied. A group of discrete firm lymph nodes, measuring 14 by 6 by 4 cm., overlaid the arch of the aorta. The cut surface of these nodes was slate gray interspersed with fine grayish pink streaks. Near the lower portion of the esophagus was a similar packet of nodes, measuring 7 by 3 by 2 cm., and similar discrete nodes were present along the upper margin of the pancreas—one node being as large as 3 cm. in the greatest diameter. The lungs and other viscera were grossly normal.

Microscopically, the cardiac lesions consisted of large areas of hyaline scar tissue, in which a few cardiac fibers persisted. The scar tissue was diffusely infiltrated, especially about its margins, with epithelial cells, lymphocytes and Langhans giant cells. Necrosis was not present, and typical compact tubercles could not be found. The lungs contained scattered tubercles, and a few miliary tubercles were found in the liver. The lymph nodes presented much the same picture as did the heart. No tubercle bacilli were found in carbolfuchsin-stained sections even after persistent search. Blocks of heart muscle were macerated for twenty-four hours in 5 per cent sodium hydroxide solution, and the residue was washed once with sterile salt solution. In the residue were found acid-fast bacilli in moderate numbers, some arranged in clumps. There were no other lesions of interest.

A few more than 200 instances of tuberculosis of the myocardium have recently been collected from the literature and reviewed by Gouley, Bellet and McMillan (*Arch. Int. Med.* **51**:244, 1933), who added 6 cases of their own. The 2 cases described by us are probably best classified as instances of tuberculosis of the myocardium of the diffuse type, in contrast to the nodular and miliary varieties. As in practically all previous cases, the tracheobronchial and mediastinal lymph nodes in each of these cases were involved, and it is probable that extension along lymphatic channels was the mode of entry. These cases differ from the majority of cases reported in the literature, however, in that the pericardium was not involved in either, and in neither was any caseation seen. A similar case has been reported by Thomson (*J. Path. & Bact.* **33**:259, 1930). Case 1 is unique in being an instance of complete heart block due to tuberculosis of the myocardium.

DISCUSSION

VERA B. DOLGOPOL: The first case for which I am showing the lantern slides was that of a Negro about 45 years of age with generalized tuberculosis, tuberculous spondylitis and a cold abscess. At autopsy a solitary tubercle about 1 cm. in diameter was found in the right side of the interventricular septum of the heart. In this case the pericardium was not involved.

The microscopic section from the second case is from a minute tubercle on the left side of the interventricular septum in a Negro boy of 13 with primary pulmonary tuberculosis and also miliary tuberculosis. That was the only lesion in the heart. The pericardium was not involved.

RUSSELL L. HOLMAN: In regard to the racial statistics on tuberculosis of the myocardium, I have been unable to go back to all of the original reports, but of the 22 cases which I have studied, 12 have been in the colored race. That is a little higher proportion than one expects, but I have not been able to analyze the cases satisfactorily.

RHEUMATIC COMMISSURAL LESIONS AND THEIR RELATION TO THE SO-CALLED CONGENITAL BICUSPID AORTIC VALVE OF THE ADULT. LOUIS GROSS.

A study of the commissures of the aortic valves from 70 rheumatic hearts disclosed characteristic lesions in the majority of them. The incidence and nature of these lesions paralleled the clinical acuity of the disease. The changes consisted of: capillarization with cellular infiltration of the aortic root in the commissural region; vascularization and cellular infiltration of the aortic wedge, with whorling of the elastic tissue; distortion and scarring of the apex of the wedge; vascularization, cellular infiltration and whorling of the collagen of the annulus; the formation of a dense collagenous zone immediately behind the aortic root and

wedge, and vascular lesions and cellular infiltrations in the pericardial mantle. The inflammatory granulation tissue could be traced as an extension by contiguity from the pericardial mantle to the aortic ring.

In order to study the pathogenesis of bicuspid aortic valves in adults, the affected commissures in 16 cases were examined for the aforementioned changes. In these cases, moreover, a search was made for microscopic and macroscopic rheumatic stigmas in other cardiac sites, and serial sections were made of the affected commissural regions with the particular object of studying inversion of the aortic wedge and whorling of the elastica and collagen fibers. Eight of the cases completely fulfilled Osler's macroscopic criteria, which have been hitherto considered sufficient to establish the congenital nature of the lesion. Eight cases fulfilled these criteria incompletely. A study of the hearts in the manner mentioned disclosed rheumatic stigmas in 14 of the 16 cases. The other 2 cases showed an association with calcific sclerosis of the aortic valve of the Mönckeberg type. Inasmuch as none of these cases showed an association with other congenital lesions and furthermore, inasmuch as a review of the reported cases indicates that the bicuspid aortic valve found in the adult is infrequently associated with other congenital anomalies, whereas that reported in the infant is practically invariably associated with other congenital anomalies, it is suggested that these findings in the adult and the infant represent two entirely different groups of lesions. The bicuspid aortic valve in the infant is generally thin and presents no appreciable evidence of inflammatory involvement. It is, therefore, probably truly congenital. The bicuspid aortic valve in the adult is almost invariably associated with a degenerative or an inflammatory lesion and is probably the result of it. The microscopic and macroscopic observations indicate that the bicuspid aortic valve of the adult is usually of rheumatic origin. This hypothesis is compatible with the well known predisposition of the bicuspid valve to subacute bacterial endocarditis.

Two cases only were observed in which there was no inversion of the aortic wedge. Faulty inversion can also be explained on an inflammatory basis.

DISCUSSION

E. LIBMAN: I have made no real study of bicuspid aortic valves. The group of specimens to which Dr. Gross has referred were collected because they puzzled me. I had a feeling that they were most likely not congenital.

Dr. Gross has referred to the fact that rheumatic valvular disease begins in the ring and then extends into the valve and often also into the pericardium. This was proved, as you know, by the studies of Dr. Gross and his co-workers. It is interesting to note that MacLagen suggested this conception, which he arrived at by just sitting down and thinking on a few practical points, without making histologic studies. His discussion of the subject is to be found in the volume published by him in 1881 (MacLagen, T. J.: Rheumatism: Its Nature, Its Pathology, Its Successful Treatment, London, Pickering & Co., 1881). It is well worthy of reading.

I wish now to stress the particular conclusion that Dr. Gross has drawn from the finished piece of work presented. There is need of a definite figure for the incidence of the bicuspid aortic valve. There is no unanimity in the figures given by the various authorities on the subject. However, I believe that one can consider an estimate of 1 to 250 persons as conservative. This would mean that there are over 500,000 persons in this country who have congenital bicuspid aortic valves. If one takes Lewis' experience as a guide, one fifth, or 100,000, of these persons will have subacute bacterial endocarditis, and nearly all these will die of it. It is probable that this figure—one fifth—is too high, because Lewis dealt mainly with soldiers who came under observation during and directly after the World War—up to 1923.

During that period there was a great increase in subacute bacterial endocarditis in all European countries from which reports are available. It is known that in civilian life the mitral valve is more frequently involved than the aortic, whereas in soldiers serving in the War the aortic valve was more often involved. Undoubt-

edly, many recruits had bicuspid aortic valves and presented no murmurs. In these recruits subacute bacterial endocarditis probably developed more readily than usual because of great mental and bodily strain, undernutrition, etc. It is important to make a study of this subject again, now that one is so far removed from that period.

I took up this subject in the Billings Lecture of 1935 and drew the conclusion that because so many of those having bicuspid aortic valves give no definite evidence of the condition a program of prevention of subacute bacterial endocarditis must include the whole population. Now that Dr. Gross has demonstrated that so large a percentage of bicuspid aortic valves in adults are due to rheumatic infection, the fate of these persons depends largely on what doctors can accomplish in the prevention of rheumatic fever.

EUGENE CLARK: I should like to ask Dr. Gross whether he finds evidence that rheumatic mitral valvulitis is commonly in association with the bicuspid aortic valve. It is my impression that this association is decidedly uncommon.

HARRY VESELL: Has Dr. Gross any statistics about the incidence of the bicuspid aortic valve in places like Puerto Rico, where rheumatic fever is infrequent?

LOUIS GROSS: Of the 16 cases on which these studies were made 3 showed an association with mitral disease, but when one speaks of mitral disease one must define what one means by the term. Those who have had considerable experience with the gross features of rheumatic hearts say that a great many show mitral disease grossly which would not be considered as doing so by those with less experience or those who employ stricter criteria. When I say that 3 of these hearts showed mitral disease I mean that the average pathologist with the average experience would be willing to admit the presence of these changes. A number of the others showed mild thickening on the free edge of the mitral valve, which it has been the custom to consider as at least suggesting a mitral process.

I do not know anything about the incidence of the bicuspid aortic valve in Puerto Rico. In the low lands of Puerto Rico rheumatic fever is apparently infrequent, and it would be most enlightening if some one could investigate this problem statistically. I have a feeling one would find few so-called congenital bicuspid aortic valves in that region.

THE PHYSIOLOGIC RESPONSE OF PROSTATIC AND VESICULAR TISSUE TRANSPLANTED INTO THE ANTERIOR CHAMBER OF THE EYE. ROBERT A. MOORE, H. B. ROSENBLUM (by invitation), S. H. TOLINS (by invitation) and ROBERT MELCHIONNA (by invitation).

Autotransplants of prostatic and seminal vesicular tissue into the anterior chambers of the eyes of rabbits were prepared by the following method. A small piece, about 2 to 3 mm. in diameter, of the desired tissue was removed through an abdominal incision and inserted into the anterior chamber of the eye through a small incision at the sclerocorneal junction. After from three to four weeks, about 60 per cent of the transplants were found vascularized and satisfactory for further study.

The transplant was photographed each day at a magnification of 25 diameters and the size determined by planimetric methods. The error of the entire method was about 4 per cent of the total size.

In otherwise normal rabbits, the size of the transplant varied considerably more than the error of the method. In rabbits in which there was viable tissue in both eyes the two transplants showed a definite, positive correlation in size. Increase in size was associated with dilatation of the vascular channels which supplied the tissue. These observations indicate that there is a daily variation in the state of the prostate, but no regular cycle can be shown.

The effects of a number of hormones have been investigated, and the results can be summarized as follows: 1. One injection of the anterior pituitary-like gonadotropic substance from the urine of pregnant women produces a marked

increase in size. 2. Subsequent injections of the gonadotropic substance have no effect. 3. Implants of beef pituitary glands and an alkaline extract of whole anterior lobe produce an increase. 4. Castration brings about a prompt decrease, the curve of which gradually loses velocity. 5. The anterior pituitary-like substance is entirely ineffective in the castrate. 6. The androgenic hormone from urine or from testicular tissue has only a slight effect in the normal animal but will stop the decrease and cause partial recovery of size in the castrate. 7. The estrogenic hormone produces a marked increase in size in both the normal animal and the castrate. 8. Androgenic and estrogenic hormones given together cause a marked increase in size, but in general the increase is no greater than that from the estrogenic hormone alone.

DISCUSSION

PAUL KLEMPERER: Dr. Moore stated that he made histologic examinations only at the beginning of the experiment, to see whether the transplants took. Were histologic examinations made to determine the appearance of the transplant during the period when it was large? I ask the question because I wonder what constitutes the enlargement. Is it cellular growth or cellular enlargement, or is it due to edema, as the transplants appeared quite vascularized?

GEORGE VICTOR: Have you studied the effects of the removal of other endocrine glands, besides the testis, on the reaction of these hormones?

IRVING GRAEF: Have you tested the effects on transplants of other tissues in the same situation?

ROBERT A. MOORE: We have not studied the gland morphologically except to see that the transplants were viable. However, when we presented the results of this investigation before one of the societies at Cornell this same question was raised, and we therefore gave 2 animals estrogenic hormone and removed the eyes at the end of the period of maximal reaction, as shown photographically. The change was one of edema and hypertrophy of the cells. There were no mitotic figures or inflammatory reaction, but there was tremendous edema, with dilatation of the blood vessels and apparent hypertrophy of the smooth muscle fibers.

The question has been brought up in regard to the use of tissues other than the prostate and vesicular tissue. We have given consideration to this because of the fact that the muscle shows marked changes under the effects of the estrogenic substance. We have been searching for an organ from which we could remove smooth muscle and determine whether nongenital tissues react to the hormone. This determination has not yet been carried out.

We have not removed any endocrine glands other than the testis.

Regular Meeting, Feb. 25, 1937

N. CHANDLER FOOT, *President*

MILTON HELPERN, *Secretary*

EXPERIMENTAL PRODUCTION OF VASCULAR LESIONS AND HEMORRHAGE IN LYMPH NODES. LEWIS HENRY KOPLIK.

Intravenous injection of filtrates from cultures of the meningococcus or the typhoid bacillus produced the Shwartzman phenomenon in the lymph nodes of rabbits which had been prepared by previous intralymphatic injection of these filtrates. The nodes receiving the filtrates showed hemorrhage, and histologically there were fibrin and platelet thrombi in the veins and capillaries. The endothelium of the thrombosed blood vessels was swollen. There was necrosis of the lymphoid tissue.

In animals in which an attempt was made to elicit the Shwartzman phenomenon in the skin with filtrates of cultures of the meningococcus or of the typhoid bacillus, the regional lymph nodes showed marked changes of a hemorrhagic character. The histologic appearance of these nodes was similar to that of the nodes in which the Shwartzman phenomenon had been produced following an intralymphatic preparatory injection. Since, according to Hudack and McMaster *(J. Exper. Med.* **57**:751, 1933), an intradermal injection may also be assumed to be intralymphatic, the mechanism of the production of the lesions in the lymph nodes in the one set of experiments is considered to be identical with that in the other. The regional nodes in rabbits showing the Shwartzman phenomenon disclosed hemorrhage and vascular thrombosis even when the sites of injection in the skin were normal. It is concluded that lymph nodes are more sensitive to the factors producing such lesions than the areas of skin which they drain.

Lymph nodes other than the regional nodes or those directly affected by the injected filtrate were normal. A single intralymphatic or a single intradermal injection of a bacterial filtrate did not produce hemorrhage or thrombosis in the regional nodes.

A single intravenous injection of a filtrate (from 10 to 25 units per kilogram) did not elicit hemorrhage or thrombosis in lymph nodes except in two rabbits infested with coccidiosis of the liver and intestines. These animals showed small multiple hemorrhages in the mesenteric lymph nodes, and, microscopically, capillary thrombi. Similar lesions were seen in the mesenteric lymph nodes of two of the rabbits which had been subjected to the procedure for eliciting the Shwartzman phenomenon. These rabbits also had coccidiosis of the gastro-intestinal tract. Such changes in the mesenteric lymph nodes were not seen in any of the rabbits showing the Shwartzman phenomenon which did not have a grossly demonstrable infestation of this type, though over 70 have been examined grossly and about half as many histologically. The case of the affected mesenteric lymph nodes may be an instance of a naturally occurring infection (coccidiosis) supplying the necessary preparatory factors for the production of the Shwartzman phenomenon in a lymph node.

In human lymphoid tissue in disease—e. g., in the mesenteric lymph nodes and lymphoid tissue of the intestine in typhoid fever—one may see hemorrhage and vascular lesions which bear a marked resemblance to those produced in the present experiment. It is suggested that since circulating toxin is probably present in the blood of such patients (Stolyhwo, N.: *J. Immunol.* **30**:235, 1936) the mechanism of the production of the lesions may be similar to that acting in the experimental elicitation of the changes in lymph nodes associated with the Shwartzman phenomenon.

DISCUSSION

RUSSELL HOLMAN: I should like to ask Dr. Koplik two questions: First, did he ever observe thrombi in the lymphatic vessels; second, how long did he observe these lymph nodes after the production of thrombi—did he ever observe any subsequent destruction of the architecture of the lymph nodes as a result of the venous thrombosis?

AMOUR LIBER: At the Lincoln Hospital we have observed a patient with chronic septicemia due to infection with Bacterium enteritidis who had lesions in multiple lymph nodes, some of which were distant from the intestine and other local lesions. There were numerous erythrophagocytes in the lymph sinuses of the affected nodes but no thromboses in the veins. It has occurred to me that there may be some explanation for these lesions in connection with the lesions which Dr. Koplik has reported. Previously we had no explanation for the erythrophagocytes. The question I should like to ask Dr. Koplik is: How long did it take the blood in the lymph nodes to be transformed into hermosiderin? My impression is that it takes longer in the lymph nodes than in the spleen.

LEWIS HENRY KOPLIK: Twice in this study of lymph nodes from over 70 rabbits I observed thrombi in the lymphatic vessels. They were not a prominent part of the picture.

I have not followed the lesions to the end-point but have observed the majority of them for only six hours after the intravenous injection. I am following them at intervals at the present time. However, in a few instances in which the rabbit was killed twenty-four hours after the intravenous injection I still found phagocytes with the red cells.

PULMONARY REACTIONS TO ASPIRATED LIPIDS. IRVING GRAEF.

Since Laughlen's report in 1925, 81 cases of pneumonia due to or associated with aspiration of various lipids have been reported, a large majority from this country. In 16 of these the diagnosis could not be proved, owing to the fact that it was based only on roentgenographic and clinical data. There are postmortem studies of 65 cases (exclusive of my series), 57 of which were in infants and young children. Adequate studies of 14 cases in infants and 2 in adults have been published, showing reasonable evidence to implicate one or more exogenous lipids. Even more thorough studies, in which an attempt was made to identify the offending lipid by extraction, have been recorded in 3 instances—2 in adults and 1 in an infant. The rest of the postmortem reports (46 cases) are deductive in the identification of the lipid and do not establish its exogenous nature beyond doubt. The findings presented here are based on a study of 17 cases observed at necropsy in the laboratory of pathology at Bellevue Hospital in the past four years; 8 were in infants and 9 in adults.

The patients were considered in two main groups: (1) infants with pulmonary changes attributable to cod liver oil and (2) infants and adults with pulmonary changes attributable to mineral oil. In 6 instances chemical extractions were done and were found to support the tentative diagnoses based on differential histochemical examination. In every instance frozen sections were stained with osmic acid, sudan IV and nile blue sulfate; unstained sections were examined polariscopically, and paraffin sections of formaldehyde-fixed and osmic acid-fixed tissue were studied with differential stains. These included stains for reticulum and fibrin, Ziehl-Neelsen stains for acid-fast substances and stains for bacteria.

There were 3 cases of pneumonitis attributable to aspiration of cod liver oil. The lungs showed patchy and confluent lobular consolidation, characterized by a fibrinopurulent exudate. One case involved the greater part of both lungs, with irregular interstitial proliferation of fixed tissue cells, and appeared to be of longer duration. Both lungs exhibited foreign body giant cells of the Langhans type and an alveolar exudate of epithelioid monocytes. All these cases were distinctively characterized by the presence of abundant acid-fast material taking the form of or appearing as membranes around large extracellular globules and also as rings or films surrounding finely emulsified droplets of the oil. The smaller forms were encountered in the foreign body giant cells and in the epithelioid monocytes. Stains for fibrin revealed that the membrane was composed of a central core of fibrillar fibrin surrounded by the lipid. In only one of these cases was a bacterial infection coexistent or superimposed. Necrosis of alveolar epithelium and walls, in one instance with cavity formation, was a striking feature in this group. Foamy macrophages were encountered in the paraffin sections of some lesions but not to any considerable extent.

The cases due to aspiration of mineral oil showed strikingly similar lesions in that the substance was dispersed in fine droplets, usually within macrophages, and in that it had accumulated in the interstitial tissue at the expense of the air sacs. In many instances the lobular architecture was obliterated, with a few rudimentary sacs as the only indication of respiratory parenchyma. In these cases the oily material was never found in polymorphonuclear leukocytes. Multinucleated foreign body giant cells were found in several cases; some of them were barely recognizable because of the great compression of the cytoplasm and nuclei by the contained globules of oil.

Although the macroscopic lesions were suspected to have an oily content in several instances, in the majority it was the finding of a massive outpouring of foamy macrophages in paraffin sections that drew attention to the presence of a lipid. In dense scars huge globules of mineral oil were found lying free in the

scar tissue. In some instances there was a marked accumulation of the oil in a web of reticulum, with the deposit remaining intracellular within individual macrophages and resembling adult adipose tissue. There was conspicuous accumulation of the offending substance around the blood vessels and bronchi. Once oil-containing cells were found enmeshed in a fibroblastic exudate like that seen in organizing pneumonia. Another conspicuous feature was a formation of lymphoid follicles in the affected areas of parenchyma. In the centers of these follicles oil-laden cells or globules were found.

Histochemical examination is a satisfactory method of identifying the offending substance, since it helps to localize it as well. In such an examination the failure to reduce osmic acid or to produce a reaction with nile blue sulfate, the absence of anisotropic globules and the production of a yellow or yellow-orange color with scarlet red all serve to identify mineral oil. The reduction of osmic acid, the appropriate reaction with nile blue sulfate, and orange-red or salmon-red reactions with scarlet red indicate the presence of other lipids.

The formation of the acid-fast membrane noted in the cases attributed to aspiration of cod liver oil was interpreted by Pinkerton, who first noted it, as a surface change in oils similar to the oxidation and formation of membrane of some drying oils when exposed to air. The studies reported here do not support this view but show that the membrane is composed of fibrin on which the oil is deposited. In later stages, when the oil is finely emulsified, the formation of the membrane is more complete; the membrane surrounds individual droplets, thus masking the presence of lipid in ordinary paraffin sections. The cellular reaction resembles that seen in the tuberculous granuloma, with an outpouring of epithelioid monocytes and the formation of Langhans' giant cells.

Clinical data confirmed the use of the offending substances in the cases attributed to aspiration of cod liver oil, in 3 of 5 cases in infants due to aspiration of mineral oil and in 6 of 8 cases in adults. Mixed lipids were responsible for some of the change in the ninth case in an adult. In the other cases no history of the use of oils was available.

Consideration of the mechanisms involved in the passage of lipids into the trachea suggests that the chief factors determining the entry of the lipid have to do with the dose and the mode of administration. The oral or intranasal administration of free-flowing oil in certain subjects may lead to its passage into the trachea. Interference with deglutition, loss of the cough or gag reflex, forced feeding, accidental entry of a gavage tube into the trachea, all these make aspiration of such an oil possible. Certain neurologic states which have in common loss or abolition of the cough reflex may promote aspiration. Even sleep may permit the passage of bland oil when this is introduced in large enough amounts to lead to free flow into the nasopharynx. Anesthesia, coma, bulbar palsy and psychotic states have been found in association with aspiration of lipids. Accidental aspiration has been noted in persons with cleft palate and in others following forced feeding, gavage feeding or persistent vomiting.

The habitual use of intranasal drops of paraffin oil, especially in large quantities and over a long period, may result in its accumulating in considerable amounts. An additional danger lies in the aspiration of such oil through its accumulation in the paranasal sinuses with subsequent discharge into the nasopharynx during sleep. Cases in which severe pulmonary changes followed therapeutic instillation of paraffin oil in the lower respiratory passages prove the difficulty of removing this material.

Certain recommendations to prevent aspiration of lipids are made. A limitation should be set on the capacity of droppers furnished with bottles of oil-containing nasal drops, and the dose for the infant or the adult should be so adjusted as to prevent accumulation and free flow of the oil into the nasopharynx when it is administered intranasally. Substitution of less irritating and more readily absorbed oils for nasal medication would diminish the injury following accidental aspiration. In view of the ease with which free-flowing oily material gains entrance into the larynx, rhinolaryngologists should reinquire into the rationale of the use of any form of such material in the nasopharynx.

Because of the difficulty of removing paraffin oil from the lung, its use as a lubricant, therapeutic agent or vehicle for medication in rhinolaryngologic practice should be stopped. The damage caused by the accumulation of even small amounts administered repeatedly over a long period is sufficiently great to warrant its replacement by other, less irritating and more readily removed lipids. And there is the added danger of the aspiration of other agents (bacteria, spores, fungi) with the oil.

DISCUSSION

N. CHANDLER FOOT: This only goes to show how slowly the wheels of progress move. Twenty-five years ago these conditions were recognized by Dr. Councilman, who noted them at the Harvard University Medical School in connection with babies dying at the Children's Hospital, who showed this giant cell macrophage pneumonia. At that time the condition was suspected to be due to the aspiration of milk by weak, marantic children and dismissed as such. Although Dr. Councilman urged those in the department to investigate it, none seems to have had the necessary energy to do so. It appears that the use of iodized poppy-seed oil 40 per cent has given the necessary stimulus, and the investigations which followed on the use, or the misuse, of this iodized oil have stimulated research into these conditions, as has been demonstrated by work on the subject, notably that of Pinkerton, to which Dr. Graef has referred. At the New York Hospital we have observed a number of such cases in the last few years, and I hope that some of the men from there will discuss them.

D. MURRAY ANGEVINE: I should like to ask Dr. Graef whether he feels that the presence of these lipids renders the lung more susceptible to a subsequent infection, or whether the person attacked gets the infection as a consequence of the debility from which he is suffering rather than from the presence of the oil, and I should also like to ask whether he has noted any changes or increase in lipid in any of the other viscera, especially the spleen and liver.

B. M. FRIED: I have been interested for many years in the reaction to oils introduced into the lungs via the trachea. Several years ago (*Arch. Int. Med.* **40**:726, 1927) Dr. Lester R. Whitaker, of Boston, and I published an experimental study of the action of iodized oil on the pulmonary parenchyma. Since then I have made supplementary reports on the action of vegetable and mineral oils introduced into the respiratory portion of the lungs by way of the trachea. The findings in man as described by Dr. Graef coincide in many ways with mine.

However, the part that I was most concerned with was not so much the destructive as the constructive reaction which the elements of the lungs displayed toward the lipoid substances. Dr. Graef has stressed the accumulation of macrophages in the interstitial tissue and alveoli of the lungs of the patient who dies following accidental penetration of oil into the pulmonary parenchyma. My experimental and clinical observations led me to the conclusion that in the early stages most of the macrophages are of local origin and that they originate from the cells lying in and on the pulmonary septums.

The problem concerning the cells lining the air sacs has produced much discussion, and for the past fifty years or so the opinions of investigators have differed. While one group of observers found that the air sacs were completely devoid of any cellular lining, others identified the lining of the septums as an endodermal epithelium and still others as mesodermal macrophages. A few lantern slides will demonstrate my point of view. [These were shown.] The sections prepared from the lungs of cats and rabbits that were killed from twelve hours to several weeks after the intrapulmonary injection of small amounts (about 2 cc.) of mineral and vegetable oils, respectively, show clearly that the first cells in the lung to be affected by the lipoid are those lying on and in the pulmonary septums. While in the normal lung these cells can barely be visualized, in the condition in these experiments they became prominent by reason of their size and structure. They instantly proliferated to such an extent as to form virtually a continuous row of cells; they detached themselves from the septums, produced pseudopodia, displayed

active phagocytosis and finally formed the bulk of the intra-alveolar exudate. By their morphologic characteristics and behavior they were identified as macrophages.

Briefly, then, the macrophages are the first cells to respond to a lipoid substance introduced into the respiratory portion of the lung. In the early stages these phagocytic cells are abundantly supplied from local sources, such as the cells lining the wall of the air sac (the so-called alveolar epithelium) and those found embedded within the connective tissue of the pulmonary septums.

IRVING GRAEF: I do not know how to answer Dr. Angevine's question concerning increased susceptibility to subsequent infection by bacteria after oil has been deposited in the lung. I imagine that such a problem might lend itself to experimental investigation. Since individual observations on human material would be subject to too many variables, I should only be guessing as to whether any of the infections were influenced by previous deposits of oil.

Visceral deposits were not seen in any of the cases, which I think is to be expected, inasmuch as the oil is not transported even to the hilar lymph nodes to any extent. In only one case was there a notable deposit in a hilar lymph node in the series.

Dr. Fried's comments on the origin of the cells participating in this reaction to lipids are interesting to me. I have hesitated, in these observations, to draw the conclusion that the proliferating cells lining the alveoli are derived from histiocytes or from wandering cells in the blood, and not from the proliferating epithelium of a terminal bronchiole. In few instances have I seen fat droplets in the alveolar lining cells. In most of the material the persistent lining cell is quite like that in the unexpanded or partially expanded alveolus of the infant.

There are many aspects to this subject, and I cannot go into them all. But I should like to refer to the need for individual study of cases—the need for careful differential studies—before a conclusion is drawn as to the nature of the offending lipid. Experiments in progress in the laboratory, done with Leo Kaplan and to be reported later, have indicated that halibut liver oil is not less irritating than cod liver oil when introduced into the trachea of an animal, and that viosterol, usually sold in corn oil, is less irritating than either oil. Of special interest in this series of observations was the polymorphonuclear response which followed the administration of very small amounts of cod liver oil. Whether that oil may be rendered less irritating, so that it produces less of an inflammatory reaction, is a question for further consideration.

MECHANISM OF INFLAMMATION. VALY MENKIN, Boston (by nvtaton).

This article is published in this issue of the ARCHIVES, page 65.

DISCUSSION

PAUL KLEMPERER: I wonder if the inflammatory reaction can be modified by changing the quantity of this crystalline substance which is recoverable from exudates; in other words, is it possible, by giving very small quantities, to produce only serous inflammation, or is any reaction followed of necessity by leukocytosis?

Another question is: What happens if one introduces the crystalline substance into the general blood stream or into a vessel supplying an organ?

RUSSELL HOLMAN: The blockage of lymphatic vessels seems to play such an important part in the series of events that Dr. Menkin has been discussing that I should like to ask three questions: First, have specific stains, such as the Gram or the Weigert stain, been made, to bring out the fibrin network; second, what subsequently happens to these fibrin thrombi, and third, has motion in these experiments been controlled? It is well known that if an extremity is kept quiet, as by placing it in a splint, there will be practically no lymph flow.

N. CHANDLER FOOT: Have you done any experiments in buffering the area of inflammation to keep the hydrogen ion concentration constant, and if so, have you noticed any consequent difference in the proportions of polymorphonuclears and monocytes?

MENDEL JACOBI: Have you noted any differences in the character or degree of fibrin formation or in its distribution in these exudates as the p_H changed? Was there any relationship between the cellular and the fibrin content, and could these changes be associated with differences in degree of glycolysis or in lactic acid content?

VALY MENKIN: In regard to Dr. Klemperer's question concerning the quantitative aspect of the problem: I have been able to obtain biologic evidence that blood serum contains the active crystalline substance but in definitely reduced concentration. The effect of blood serum or of its fractions on the permeability of the endothelial wall is of a distinctly lower grade as compared with the extensive filtration of plasma induced by an exudate or by the active crystalline substance recovered from it. Only by diluting an exudate can the reaction on the capillary wall be made to resemble in intensity that elicited by undiluted blood serum. When the latter or the crystalline material recovered from blood serum is inoculated into tissues, leukocytic migration is hardly a conspicuous accompaniment in the interval studied (i.e., from twenty-five to forty minutes). This suggests that perhaps *lowering* the concentration of the active crystalline substance recovered from exudates is less likely to produce in a given time as active a migratory effect on the leukocytes. I realize that this answer is indirect and therefore inadequate. A study of the quantitative phase of the problem is on my program, but as I observed this effect on leukocytic migration only several weeks ago I simply have had no time as yet to work out all the interesting quantitative points, including the question Dr. Klemperer brings up in regard to the mechanism of a serous inflammation. Likewise, the effect of intravascular injections of the active crystalline substance has not been adequately studied as yet, although plans are being made to do so in the near future. A preliminary injection of a small amount of the material into the vein of a rabbit's ear has failed to produce any manifest toxic effect. This phase, however, will soon be investigated more thoroughly. In a few weeks I shall perhaps be in a position to bring forward some concrete information on all these interesting questions.

In regard to Dr. Holman's questions on lymphatic blockades: 1. Preparations have been made with Weigert's stain to bring up more adequately the network of fibrin. 2. The ultimate resolution of lymphatic thrombi in inflammation is not yet fully clear, as I have scarcely studied the reparative processes following the acute inflammatory reaction. It is conceivable that enzymatic autolysis and heterolysis may play a rôle. The p_H of the lymph draining an inflamed area should perhaps be measured as well as that of the exudate. Such a study might provide a lead in regard to the liberation of enzymes which are active at various hydrogen ion concentrations and which may thus induce resolution of thrombi. 3. In the experimental procedures, motion is maintained. As soon as an animal is given an injection of an irritant, it is released from any hold and allowed to run freely around its cage or even on the laboratory floor.

In regard to Dr. Foot's question on the buffering of an area of inflammation: I have encountered, in attempting to do so, considerable difficulty. I have repeatedly failed to maintain a constant p_H by the injection of Sorensen buffers. The local reaction developed to an acid p_H irrespective of whether one injected into the inflamed area an alkaline phosphate buffer, solid magnesium carbonate or iodo-acetic derivatives. The latter were utilized to prevent the formation of lactic acid. The observations indicate that tissue buffers and their control are still sadly in need of investigation.

In answer to Dr. Jacobi's questions: The extent of the deposition of fibrin seems to increase, within limits, with the progress of the inflammatory reaction. This deposition appears to take place up to a certain point in the initial stages of the reaction, but whether it can be correlated in any way with the increase in hydrogen ion concentration is not clear. Further studies on this question will doubtless be necessary. There has been in my experience no definite evidence of relationship between the cellular and the fibrin content.

PATHOLOGICAL SOCIETY OF EASTERN NEW YORK

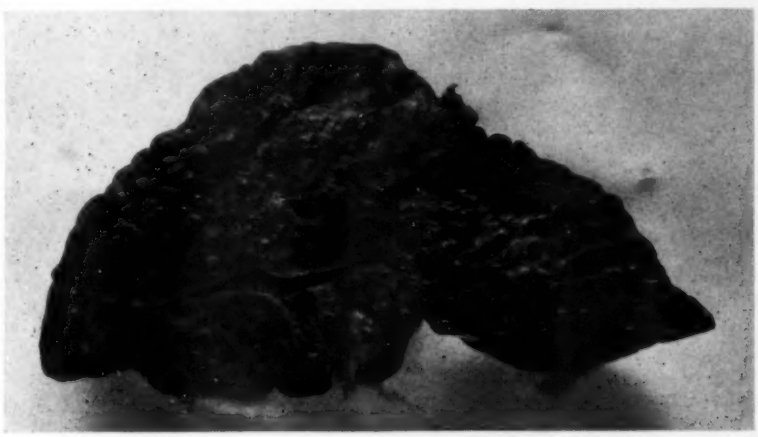
Regular Meeting, March 13, 1936

MORRIS MASLON, *Presiding*

ARTHUR W. WRIGHT, *Secretary*

CIRRHOSIS OF THE LIVER IN A CHILD. ELLIS KELLERT.

A girl 12 years old, whose past history was unimportant, entered the hospital because of slight jaundice, as well as swelling of the legs and face. In addition to these symptoms, she was found to have marked ascites. There was no fever. The urine was not abnormal. A positive direct van den Bergh test was obtained on the blood serum. The blood Wassermann reaction was negative. Moderate secondary anemia was present. A diagnosis of cirrhosis or new growth of the liver was made and laparotomy performed. A large amount of bright yellow



Cirrhotic liver of a girl 12 years old.

fluid was found in the peritoneal cavity. The liver was small, hard and nodular. No tumor was observed. The patient died several days later.

At necropsy the chief pathologic changes were found in the liver and spleen. The liver measured 16 by 11 by 8 cm. and weighed 855 Gm. Its consistency was greatly increased, and the surface was markedly nodular, firm and greenish brown. Nodules of greenish soft hepatic tissue of varying size protruded above the surface and were separated by broad bands of dense fibrous tissue. The gallbladder was normal, and the bile passages were patent.

Microscopically, the most outstanding feature was the large size of the hepatic lobules, in which the cells presented a normal appearance. The sinusoids were congested, and the Kupffer cells were prominent and filled with pigment granules. There was very little intralobular connective tissue. Between the lobules were broad bands of dense fibrous tissue containing a variety of leukocytes, remnants of polygonal cells and bile ducts. The increased periportal connective tissue was extremely pronounced in some areas.

The spleen measured 16 by 10 by 6 cm. in size and weighed 510 Gm. Its color was normal and its density increased. The cut surfaces had a dark red hemorrhagic character. Microscopic examination showed intensely congested pulp with greatly increased numbers of polymorphonuclear leukocytes. The fibrous trabeculae were not prominent. The lymph nodules were greatly atrophied.

FATAL INTESTINAL OBSTRUCTION DUE TO A BILIARY CALCULUS. V. W. BERGSTROM.

A white man aged 67 years entered the hospital complaining of abdominal distention which had been present for three days. The bowels had not moved for a week. There had been some belching and borborygmi, but no feces, flatus or blood had been passed. There was no history of vomiting, jaundice or any other symptom relative to the gastro-intestinal tract. Roentgen examination revealed complete obstruction at the rectosigmoid junction. This was believed to be due to carcinoma.

At operation, a foreign body could be palpated in the lumen of the large intestine. An attempt to manipulate it into the rectum failed, and when the colon was opened, a large biliary calculus was found. The patient did not survive the operation.

At autopsy, the rectal wall was so markedly thickened that the lumen was almost occluded. Grossly, the changes appeared to be not neoplastic but rather inflammatory. Numerous small diverticula were found. In one place a pocket of inspissated feces with no apparent connection with the lumen of the bowel was discovered. An open fistulous tract, obviously old, was found between the gallbladder and the transverse colon. The cystic duct could not be demonstrated, but at the proximal end of the gallbladder was found a calculus which was faceted in such a way that it exactly matched the faceted end of the calculus found in the colon. Chemical examination of both calculi showed them to be composed of cholesterol and bile pigment.

MULTIPLE MYELOMA: REPORT OF A CASE. J. SCHLEIFSTEIN.

Multiple myeloma is a well recognized clinical and pathologic entity and is no longer considered rare. The most striking features have been clearly described by Ewing and more recently by Geschickter and Copeland. The following case is presented because of certain atypical symptoms. Clinically, the condition simulated multiple metastases to the bone, and the diagnosis was established only at necropsy.

The patient, a man 53 years old, a cook, was admitted to the hospital with a fracture of the right femur. Roentgen examination revealed a peculiar mottling in the region of the fracture. Within a short time, symptoms suggestive of bronchopneumonia developed; they were, however, of only a few days' duration. A roentgenogram showed diffuse mottling of the lower ribs. While the patient was still in the hospital, a fracture to the left femur occurred which on roentgen examination appeared to be similar to that of the right. A roentgenogram of the skull revealed a few round areas of bone destruction, which tended to unite. Marked albuminuria was present; also, secondary anemia with slight leukocytosis. No test was made for Bence-Jones protein. A clinical diagnosis of multiple bone metastases from a possible primary carcinoma of the gastro-intestinal tract was made.

At autopsy, no tumor of the thoracic or abdominal organs was found, but examination of the femurs showed hemorrhagic tumors of the marrow of both bones. A section from the upper third of the right femur, measuring 12.5 cm. in length, and a section from the middle third of the left, 10 cm. in length, were submitted for examination. These sections presented similar pictures. In some areas, the cortex was notably thinned out and could be cut with a stout knife; in others, it was completely destroyed. The bone marrow was almost totally replaced by the tumor, which was soft and grayish and showed foci of hemorrhage. At some points, it had broken through the cortex and invaded the surrounding tissues. Sections taken from several portions of the tumor showed a typical plasma cell myeloma.

CONGENITAL ANEURYSM OF THE CIRCLE OF WILLIS: REPORT OF A CASE. A. W. WRIGHT.

A 40 year old married woman who had been ill with a slight cold for several days had a severe coughing spell shortly after arising. When the attack was over,

she complained of excruciating headache, dizziness and numbness in the legs. In a few minutes she lost consciousness. A half hour later a physician found her cyanotic, in coma and breathing very irregularly. In less than an hour death resulted, apparently from respiratory paralysis. The heart continued to beat for some minutes after respiration had ceased.

At autopsy, an elongated, somewhat constricted saccular aneurysm of the circle of Willis was found. It was present, as the accompanying sketch shows, just at the point at which the left internal carotid artery joins the circle of Willis. The aneurysm had ruptured in the posterior portion of the sac, where the wall was thin and delicate. Extensive subdural and subarachnoid hemorrhage was present at the base of the brain as well as over the ventral and lateral surfaces of the left hemisphere. A small focus of softening was found in the adjacent cortex of the left temporal lobe.

Drawing of the base of the brain to show an aneurysm of the circle of Willis. Note the site of rupture at the posterior pole of the sac.

An aneurysm of the circle of Willis is sufficiently uncommon to warrant this brief report. In most of the cases it is congenital and may be due, as Eppinger has suggested, to congenital weakness of the medial coat of the vessel. This theory appears to be borne out by the fact that in most of the cases, including the present one, the aneurysm occurs where the affected vessel bifurcates. The entire brain was saved intact in this instance, and microscopic studies of the arterial wall were not made.

THORACIC LYMPHOBLASTOMA IN A CHILD. F. F. HARRISON.

A boy of 11 was admitted to the hospital with a chief complaint of bulging of the lower part of the sternum. The child proved, on examination, to have a large mediastinal mass, apparently originating in the region of the thymus gland, with signs in the right side of the chest referable to impingement on the bronchi of the right lung. There were small nodes palpable above both the clavicles in the cervical region. Several nodes were also present in the axillae. A small

mass could be felt in the suprasternal notch. The spleen could not be felt. The original examination of the blood showed hemoglobin 70 per cent, the erythrocyte count 3,800,000, and the leukocyte count 21,000. A differential count revealed that 86 per cent of the cells were polymorphonuclear leukocytes, 12 per cent small lymphocytes and 2 per cent large lymphocytes. Roentgen examination of the chest disclosed a large mediastinal mass with secondary changes in the lungs.

Microscopic examination of one of the enlarged cervical lymph nodes showed histologic changes typical of Hodgkin's disease. Sections were referred, however, to a number of pathologists in the eastern part of the United States, and there was some disagreement as to the diagnosis. While the greater number of these men believed the condition to be Hodgkin's disease, there were several who felt that the primary new growth was a thymoma. The diagnosis of Hodgkin's disease was believed to be correct.

The boy was treated intensively with roentgen rays of high voltage but had subsequent recurrences in the cervical lymph nodes and upper mediastinum for the next year and a half, since which time there has been an interval of four and a half years without roentgen therapy and with no signs of recurrence. As far as can be determined, the patient is perfectly well, six years after he was first seen.

This case is of especial interest because of the original disagreement in diagnosis and because of the apparent cure of Hodgkin's disease as a result of treatment with roentgen rays of high voltage.

RETICULUM CELL SARCOMA: A REPORT OF TWO CASES. F. F. HARRISON.

A carpenter 74 years of age entered the hospital with a history of a lump in the neck of six weeks' duration. This lump had rapidly increased in size until at the time of admission it was as large as a baseball. From the lump an indurated extension could be palpated extending downward toward the suprasternal notch. Enlarged lymph nodes were also felt in both axillae and groins. The hemoglobin was 80 per cent. The erythrocytes numbered 3,480,000 and the leukocytes 31,000, and a differential count showed polymorphonuclear leukocytes 86 per cent, small lymphocytes 4 per cent, eosinophils 7 per cent, large lymphocytes 2 per cent and monocytes 1 per cent.

A biopsy specimen taken from the tumor mass showed replacement of the normal lymphoid tissue by a loose stroma, which was infiltrated by large pale-staining cells with occasional large multinucleated cells. Many mitotic figures were present. The spindle cells which formed the reticulum of the node seemed to shade off into the neoplastic cells. There were many foci of necrosis. A diagnosis of reticulum cell sarcoma was made.

The patient received massive doses of roentgen rays of high voltage with absolutely no evidence of regression. He went rapidly down-hill, dying four weeks after admission. The total duration of life from the time that a very small pimple-like area was felt was less than three months.

At autopsy, an extension of the neoplasm into the superior mediastinum was found, with invasion of the left jugular and innominate veins. There were multiple metastases in the lungs.

The second case was that of a farmer 66 years old, who was admitted to the hospital with a chief complaint of a lump in the left inguinal region of one month's duration. Two and a half years previously he had walked into the edge of a table, striking himself in the groin. Four months later he first noticed a nontender lump in this region. The lump was removed surgically, and radium treatment was given. The pathologic report received from the hospital where this operation was performed indicated that the tumor was a nevus cell carcinoma. The immediate effect of treatment with radium and operation was apparently successful. Radium was again used a year later, and after that the patient was free from symptoms until one month before the present admission.

Physical examination showed some enlargement of the inguinal lymph nodes in the left lower quadrant of the abdomen and a smooth firm tumor mass, which extended from 3 to 4 cm. above the inguinal ligament and medially nearly to the

symphysis pubis. Neither the mass nor the enlarged inguinal lymph nodes were tender. The hemoglobin was 75 per cent. The erythrocytes numbered 4,100,000, the leukocytes 12,450, per cubic millimeter. A differential count showed 67 per cent polymorphonuclears, 22 per cent small lymphocytes, 10 per cent large lymphocytes and 1 per cent eosinophils. The stools consistently contained occult blood.

A lymph node removed for microscopic examination showed replacement of the normal structures by round or polyhedral cells with pale-staining cytoplasm and large vesicular nuclei, which varied considerably in depth of staining. Moderate numbers of mitotic figures were observed. A fine reticulum appeared to be somewhat more plentiful than that in a normal lymph node and seemed to be in fairly close relationship to the tumor cells. Rarely did one of the cells have more than one nucleus. A diagnosis of reticulum cell sarcoma was made.

The patient was treated with roentgen rays of high voltage with little benefit and was discharged soon afterward with a draining sinus at the site of operation.

Book Reviews

The Lung. By William Snow Miller, M.D., D.Sc., Emeritus Professor of Anatomy, University of Wisconsin. Price, $7.50. Pp. 209, with 152 illustrations, 19 of them colored. Springfield, Ill., and Baltimore: Charles C. Thomas, Publisher, 1937.

Miller completed his book and wrote its preface on Sept. 15, 1934, but it is fitting that an unintentional delay caused it to leave the press at the beginning of 1937; for exactly fifty years ago he began his initial research on the lung. Among scientists who have had the good fortune to live with unimpaired vigor and enthusiasm to and beyond the biblical span of three score years and ten, Miller stands unique because for half a century from the day when he launched forth as an investigator he has held unswervingly to the same course and subject of search. His incentive to the study of the lung began in 1887 while he was at the College of Physicians and Surgeons in New York, where Francis Delafield advanced the view that there were free communications between the air spaces in that organ. This thesis seemed to be confirmed by the wax corrosions of the lung prepared by J. West Roosevelt. Miller was led to choose it as the subject of his work in the laboratory of Franklin P. Mall, at Clark University, Worcester, Mass., who had Miller as his first assistant. Making numerous corrosions in wax and Wood's metal and dissecting them, Miller discovered that the form, arrangement and relations of the terminal divisions of the respiratory tree did not agree in detail with the view held regarding them. He found the part in the divisions to which he eventually gave the name "atrium," the segment interposed between the alveolar duct and the alveolar sac. This observation was the start of his labors which gave a correct conception of the minute architecture of the lung. Another phase of the work was begun several years later, which had as its object the precise charting of the lymphatics throughout this organ. In the meantime he had entered on his active period of instructions at the University of Wisconsin (1892-1924). During this period he took one year to give undivided attention to his problem in the laboratory of Spalteholtz at the University of Leipzig, and another year he spent at Johns Hopkins University.

Since the close of his instructional duties, Miller has continued with unflagging interest his studies on the lung, making important contributions on the borderland between its normal and its pathologic anatomy. But in his book he discusses essentially the normal organ—a restriction which may vex the pathologist at first. Disappointment soon gives way to commendation as perusal of the book reveals how solidly the basic morphologic facts are marshaled for the interpretation of abnormal conditions.

The material is presented in twelve chapters. Almost all of them deal with the minute anatomy of the lung and are based squarely on Miller's own work. Space forbids discussing their content or their wealth of original observations and new illustrations in detail. When he comes to the alveolar epithelium, one cannot conceal a bit of disappointment, mingled with a larger share of spontaneous admiration, because of the short work he makes of the well known controversy pertaining to its nature; true, he presents the earlier steps in the historical development of the conceptions, but alludes only in passing to the antagonisms of the theories denoted by the words "septal cell" and "unbroken alveolar epithelium." From his observations of the behavior of the lining of the air sacs and alveoli during certain pathologic processes in the lung, Miller is convinced that a continuous alveolar epithelium exists in the adult human lung.

Regarding the lympathic drainage of the lung, it may be permitted to comment on data which are presented by Miller for the first time and to voice the opinion that he gives undue space, perhaps, to the discrepancy between certain other

findings on the distribution of the lymphatic valves in the lung of the human fetus and his own observations on the lung of a child 9 weeks old. In a study of serial sections of sample blocks from the fetal specimen, he found a relatively great number of valves in the lymph channels of the pleura on the mediastinal side next to the heart, fewer on the diaphragmatic surface and on the mediastinal surface adjacent to the heart. Miller finds these differences strange, although he remarks that it may not be improbable that there is a proportional increase in the number of valves at the apex of the lung, for example coincident with the increase in the functional activity of the organ. It seems evident now that the significance of this physiologic shift has not been understood sufficiently clearly. For it is obvious that the relative differences in pressure on the pulmonary surfaces are quite different when the prenatal and postnatal periods are compared. Further studies are needed to establish how these natal changes affect the differentiation of the lymphatic drainage routes.

Incidentally, attention must be directed to a slip of Miller's pen with its consequence of later confusion; when he speaks of the "costal, mediastinal, and diaphragmatic pleura" he does not mean the parietal pleura lining the pleural cavity but the corresponding areas or surfaces of the pulmonary or visceral pleura.

A subject which in most histologic treatises on the lung is passed over lightly, namely, the pulmonary lymphoid tissue, Miller treats adequately. Reference is made to one of his many observations, namely, the definite increase—contrary to the tendency elsewhere in the body—of the lymphoid tissue in old age. This increment is independent of that which may be produced by inflammatory diseases and is dependent on the amount of carbon or other irritating particles inhaled.

Presented in fascinating style is the matter in chapter 11, which gives historical sketches with reproductions of the original figures of the different conceptions held regarding the structure of the lung from the time Vesalius described it in 1543 to the present. Confining himself in these portrayals to the arrangement of the air spaces, he furnishes in chronological order the descriptions and diagrams of Malpighi, Thomas Willis, Francois Reisseiessen, Everard Home, Dominigue-Auguste Lereboullet, Antoine Bazin, Jean-Marc Bourgery, Jachim Giraldès, Thomas Addison, George Rainey, Hippolyte Rossignol, Jacob Moleschott, Louis Mandl, Arius Adriani, Ernestus Schultz, Albert von Kölliker, Robert Bentley Todd, William Bowman, Thomas Williams, Houghton Waters, Joseph von Gerlach, Franz Schulze, William Turner, Georg Rindfleisch, Jean Martin Charcot, Ludwig Stieda, E. Laguesse, Henri Berdal, A. Nicolas, H. Loeschcke and Hermann Braus.

In addition to the figures from Miller's papers, which already have found a permanent place in textbooks and reference works, there are more in this book which, the reviewer predicts with certainty, will enjoy even greater "popularity," so laden with facts and therewithal so graphic and self-explanatory are they. These illustrations are: Figures 6 (carinal cartilage); 8 (musculus trachealis); 18 (bronchiolar muscles); 28 (terminal branchings of the bronchial tree); 38 and 39 (distribution of elastic fibers); 54 (primary lobule with subdivisions of bronchial tree, blood and lymph vessels and sites of lymphoid tissue—"key points"); 60 (bronchiolar capillary network); 92 (distribution of nerves); 95 to 99 (nerve endings), and 151 (section of secondary lobule).

There are 222 bibliographic references. Although these by no means exhaust the literature pertaining to the normal morphology of the lung, they are dominantly representative and contain a wealth of additional bibliographic data.

Miller's book will be among the most used reference works in medical libraries. It should inspire other anatomists to achieve something comparable on other organs of the body.

Books Received

THE PATIENT AND THE WEATHER. William F. Petersen, M.D., with the assistance of Margaret E. Milliken, S.M. Volume IV, Part I, Organic Disease: Cardio-Vascular-Renal Disease, Including a Chapter on Experimental Endocarditis by Alexander J. Nedzel, M.D., Associate Professor in the Department of Pathology, Bacteriology, and Public Health, University of Illinois College of Medicine, Chicago. Cloth. Price, $10. Pp. 663, with 443 illustrations. Ann Arbor, Mich.: Edwards Brothers, Inc., 1937.

MEDICINA FENNICA XI ANNO MCMXXXV. Edidit Societas Medicorum Fennica Duodecim. Auxilio Professoris Ordin. Universitatis Gösta Becker. Redigenda Curavit Atle M. Mali. Pp. 201. Helsinki, Finland: Suomalaisen Kirjallisuuden Seuran Kirjapainon Oy, 1937.

HISTOCHIMIE ANIMALE. MÉTHODES ET PROBLÈMES. L. Lison. Avec une préface de Pol Gérard. Paper. Price, 50 francs. Pp. 320. Paris: Gauthier-Villars, 1936.

LEGAL MEDICINE AND TOXICOLOGY. Thomas A. Gonzales, M.D., Acting Chief Medical Examiner, New York City; Associate Professor of Forensic Medicine, New York University; Milton Helpern, M.D., and B. M. Vance, M.D., Assistant Medical Examiners, New York City; Lecturers in Forensic Medicine, New York University. Foreword by Harrison S. Martland, M.D. Cloth. Price, $10. Pp. 754, with 244 illustrations. New York: D. Appleton Century Company, Inc., 1937.

THE ENDOCRINES IN OBSTETRICS AND GYNECOLOGY. Raphael Kurzrok, Ph.D., M.D., Associate in Obstetrics and Gynecology, College of Physicians and Surgeons, Columbia University. Cloth. Price, $7.50. Pp. 488, with 178 illustrations. Baltimore: Williams & Wilkins Company, 1937.

COLLECTED REPRINTS FROM THE LABORATORIES OF THE MOUNT SINAI HOSPITAL, NEW YORK. Louis Gross, M.D., Director, 1936. Various pagination.

BACTERIOLOGY OF SPECIFIC COMMUNICABLE DISEASES. HANDBOOK OF PUBLIC HEALTH BACTERIOLOGY. GENERAL INFORMATION REGARDING EPIDEMIOLOGY, COLLECTION AND SHIPMENT OF SPECIMENS, AND BACTERIOLOGIC, SEROLOGIC AND CHEMICAL PROCEDURES, 1937. Edited by M. S. Marshall. Paper. Pp. 141. San Francisco: J. W. Stacey, Inc.